RESEARCH ARTICLE

Comparative Study on Transcatheter Arterial Chemoembolization, Portal Vein Embolization and High Intensity Focused Ultrasound Sequential Therapy for Patients

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Abstract

Objective: To investigate the safety and efficacy of transcatheter arterial chemoembolization (TACE), combined with portal vein embolization (PVE), and high intensity focused ultrasound (HIFU) sequential therapy in treating patients with hepatocellular carcinoma (HCC). Methods: Patients with inoperative HCC were treated by two methods: in the study group with TACE first, then PVE a week later, and then TACE+PVE every two months as a cycle, after 2~3 cycles finally HIFU was given; in the control group only TACE+PVE was given. Response (CR+PR), and disease control rate (CR+PR+SD), side effects, overall survival and time to progress were calculated. Results: Main side effects of both groups were nausea and vomiting. No treatment related death occurred. In the study group, 32 patients received TACE for overall 67 times, PVE 64 times, and HIFU 99 times; on average 2.1, 2 and 3.1 times for each patient, respectively. In the control group, 36 patients were given TACE 78 times and PVE 74 times, averaging 2.2 and 2.1 times per patient. Effective rate: 25.0% in study group and 8.3% in control group ($p>0.05$). Disease control rates were 71.9% and 44.4%, respectively ($p<0.05$). In patients with portal vein tumor thrombus, the rate reduced over 1/2 after treatment was 69.2%(9/13) in the study and 21.4%(3/14) in the control group ($p<0.05$). Rate of AFP reversion or decrease over 1/2 was 66.7%(16/24) in study and 37%(10/27) ($p<0.05$) in control group. Median survival time: 16 months in study and 10 months in control group. PFS was 7months in study and 3 months in control group. Log-rank test suggested that statistically significant difference exists between two groups ($p=0.024$). 1-, 2- and 3-year survival rates were 56.3%, 18.8% and 9.3% in study, while 30.6%, 5.6% and 0 in control group, respectively, with statistically significant difference between two groups (by Log-rank, $p = 0.014$). Conclusions: The treatment of TACE+PVE+HIFU sequential therapy for HCC increases response rate, prolong survival, and could thus be a safe and effective treatment for advanced cases.

Keywords: HCC - transcatheter arterial chemoembolization - portal vein embolization - high intensity focused ultrasound

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common and fatal gastrointestinal malignancies (Parkin DM et al., 2005; Bridges et al., 2011; Kamsa-ard et al., 2011). The incidence of HCC in China is particularly high, accounting for 55% of all cases diagnosed worldwide (Hua et al., 2011). The majority of HCC patients present with advanced disease that is not amenable to resection; 84% with extensive intrahepatic disease do not undergo any resective or ablative therapy. However, there has been an increase in the use of noninvasive local and regional therapies in recent years (Schwarz et al., 2008).

Transcarterial chemoembolization (TACE) is a recognized preferable non-surgical treatment in this setting of paitents (Kim et al., 2012). In fact, 20%~50% of tumor tissue necrosis completely after TACE; even after repeated TACE, there are still cancer cells remaining, and the 5-year survival rate is only 9%~16.2% (Zhou et al., 2011). The explanation is assumed that portal vein participates in tumor nutritional supply, and the formation of portal vein tumor thrombus and residual tumor attributes to disease recurrence (Zhou et al., 2011).

Portal vein embolization (PVE) is reported a method delivering chemotheraputic agents directly to the most active marginal zone of the tumor and meanwhile block the portal vein that nourishs the tumor (Pan et al., 2001). Primary tumor and the sub-focus of PHC could undergo complete necrosis when PVE is combined with TACE (Pan et al., 2001). Thus, TAE+PVE is hypothesized to be an ideal method for the treatment of unresectable advanced HCC. In clinical practice, intermission period of TACE is relatively long, and 2~3 TACE is ususally recommended, so many complications of patients always increase with

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frequent TACE (Zhou et al., 1998). How to maximize treatment efficacy and not to increase side effects is a main concern for medical oncologist. In recent years, new treatment modality with mechanism different with TACE and PVE is supposed to play a role in this field. High intensity focused ultrasound (HIFU) is one of such consideration. When solid tumor is exposed under HIFU, the target tissue will demonstrate coagulation necrosis, and apoptosis. Mechanism of HIFU as a therapy is based on the soft tissue penetration, and biological effects, eg., high temperature, cavitation erosion as well as mechanical destructiveness of ultrasound when it is focused on tumor tissue. On this background, we hypothesize that TAE combined with PVE and HIFU as a treatment plan could greatly enhance treatment effect for hepatic cancer, and not increase treatment related side effects.

Materials and Methods

General Information

During Jan. 2000 to Jun. 2006, patients with inoperable HCC were recruited into this research and divided into study and control group. All patients participating in the research were in line with the diagnostic criteria of Chinese Anti-Cancer Association for HPC (Society of Liver Cancer CACA., 2000).

Methods

Patients in study group were treated with TACE combined with PVE and HIFU, while patients in control group were treated with TACE and PVE.

TACE is employed with Seldinger Technique. Insert 5F catheter into common hepatic artery, and super-select proper hepatic artery after tumor vessel being determined through angiography. Then chemotheraputic agents (5-fluorouracil, cisplatin, and epirubicin) and embolic agents (Lipiodol, adding gelatin) are injected. TACE is conducted every 2 months, and designating 2~3 TACE as one course.

PVE is carried out 1 week after TACE. Positioned by B-ultrasound, corresponding branch of portal vein is selected as puncture targets. After local anesthesia with lidocaine, stick 22G paracentetic needle into the liver. Then pull out the stylet with blood flowing out of, confirming that the needle is in portal vein. Chemotherapy drugs (being the same as TAE, but the dosage being reduced to one half or one third) and embolic agents (2~10ml of Lipiodol) are injected. Finally, dress with pressure for 10h. Hepatic radiographic films of patients are recorded.

HIFU is performed 2 weeks after TACE and PVE. Treatment parameters of HIFU, FEP-BY02, from Beijing Deyuan are as follow: (1) electrical power input: 1~2KW; (2) unit launch time: 150ms; (3) account for empty: 150ms; (4) launch times on each point: 50 times, and treatment time: 30 ~ 60min. Depending on tumor size, the treatment should be repeated for 2~10 times.

Follow-up

All patients underwent out-patient or telephone follow-up. Survival time of patients was determined from diagnosis to date of death or last follow-up, and all patients were available during follow-up.

Evaluation of response

Size of tumor and/or portal vein tumor thrombus, value of AFP, treatment-related side effects and survival rates of two groups were documented by licensed medical oncologists. Objective response were evaluated according to RECIST criterion, including complete remission (CR), partial remission (PR), stable (SD) and progression of disease (PD). Response rate(RR) was calculated by (CR+PR)/(CR+PR+SD+PD), disease control rate (DCR) was calculated by (CR+PR+SD)/(CR+PR+SD+PD). Overall survival (OS), progression-free survival (PFS), were calculated by Kaplan-Meier method. Toxic reactions were evaluated according to National Cancer Institute-Common Toxicity Criteria (NCI CTC), including Grades 0~4.

Statistical method SPSS statistical package (version 11.5) was used. Data between groups were analyzed by χ^2 test, and survival analysis by Kaplan-Meier method. We have enough experience in conducting medical researches, and have published some results elsewhere (Huang et al., 2004; Zhou et al., 2009; Jiang et al., 2010; Yan et al., 2010; Gao et al., 2011; Huang et al., 2011; Li et al., 2011; Li et al., 2011; Li et al., 2011; Xu et al., 2011; Xu et al., 2011; Xu et al., 2011; Yan et al., 2011; Zhang et al., 2011; Gong et al., 2012; Li et al., 2012; Yu et al., 2012).

Results

There were 32 patients in study group and 36 in control group. Portal vein tumor thrombus mainly located in intrahepatic I~II branches. The differences of physical condition, age, hepatic function, tumor number and size, AFP titer and portal vein tumor thrombosis between two groups were not statistically significant ($p>0.05$) (Table 1).

In study group (32 patients), 67 times of TACE (2.1 times/patient), 64 times of PVE (2 times/ patient), 99 times of HIFU (3.1 times/ patient) were conducted; while in control group (36 patients), 78 times of TACE (2.2times/ patient), 74 times of PVE (2.1 times/ patient).

Table 1. Patients General Characteristic

Parameters		Study Group (n=32)	Control Group (n=36)
Gender	Male	24	26
	Female	8	10
Age(year)	Range	35-70	40-65
	Median age	55	53
Child-Pugh	A	28	32
	B	4	4
AFP	Positive	24	27
	Negative	8	9
Tumor	Single	25	29
	Multiple	7	7
Diameter(cm)	Range	5.1-12.3	4.0-15.3
Vein tumor thrombus	Yes	13	14
	No	19	22

Table 2. Treatment Response of Two Groups (%)

	CR	PR	SD	PD
Study Group (n=32)	0 (0/32)	25 (8/32)*	46.9(15/32)	28.1 (9/32)
Control Group (n=36)	0 (0/36)	8.3(3/36)	36.1(13/36)	55.6(20/36)

CR, complete remission; PR, partial remission; SD and PD, stable and progression of disease

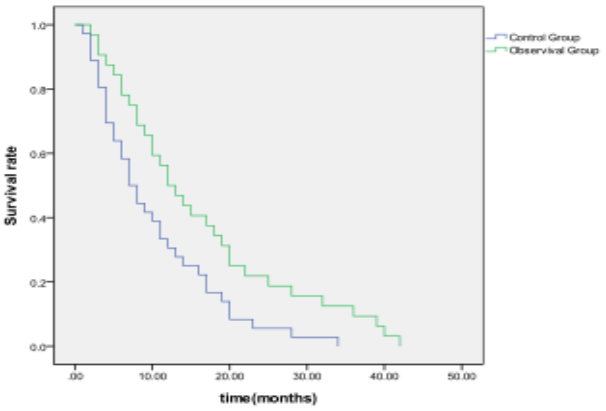

Figure 1. Overall Survivals

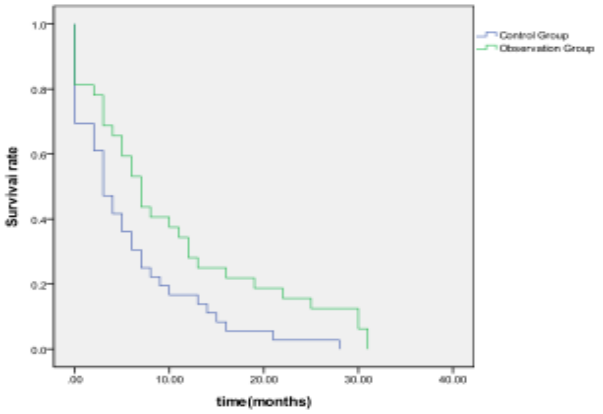

Figure 2. Progression-free Survivals

Evaluation of RR

RR was 25.0% in study group and 8.3% in control group (χ^2=2.35, p>0.05); Disease control rate was 71.9% in study group and 44.4% in control group, significant higher in study group (χ^2=5.21, p<0.05) (Table 2).

Changes of portal vein tumor thrombus

Patients with portal vein tumor thrombus in study group whose tumor embolus decreased by 50% in size occupied a percentage of 69.2% (9/13), while patients in control group 21.4% (3/14). And the difference between the two groups were significant (χ^2=8.32, p<0.01).

Changes of AFP

Patients in study group whose AFP turned negative or decreased by 50% occupied a percentage of 66.4% (16/24), while patients in control group 37% (10/27). And the difference between the two groups were statistically significant (χ^2=4.46, p<0.05).

Survival time

Median survival time: 16 months in study group (95%CI: 12~20 months) and 10 months in control group (95%CI: 7~13 months). 1-, 2- and 3-year survival rates:

Table 3. Side Effects in Two Group

Parameters	Study group Group	Control Group
Nausea	22	24
Vomiting	13	11
Fever	9	8
Pain	16	14
Leucocytopenia	20	19

study group were 56.3%, 18.8% and 9.3% respectively; while control group 30.6%, 5.6% and 0 respectively. Log-rank test suggested that there were significant difference in OS between two groups (χ^2 = 6.320, p = 0.014) (Figure 1). PFS: 7months in study group (95%CI: 5~9 months) and 3 months in control group (95% CI: 1~5 months). And Log-rank test suggested that there were significant difference between two groups (χ^2 =5.340, p=0.024) (Figure 2).

Side effects

After treatment of TACE, patients presented varying degrees of embolization syndrome, such as nausea, vomiting, fever and liver pain, which may be avoided or mitigated when non-steroidal anti-inflammatory analgesic and antiemetic agents were given to. There was less side effects of PVE carrying out through B ultrasound-guided percutaneous liver fine needle aspiration were less. Only a small number of patients presented mild pain in the puncture site after the operation. There were no nausea and vomiting during the operation, and no pneumothorax, hemothorax, hepatic subcapsular hematoma, intra-abdominal hemorrhage and perforation bleeding in intercostal arteries. HIFU side effects: 78% (25/32) of patients presented local pain during and after treatment, 18 cases of whom needed narcotic analgesics to relieve pain, 8 cases presented skin burns (Degree I ~ II), and no cases presented injuries of biliary tract, lung and gastro intestine as well as tumor rupture and bleeding, etc. White blood cells of patients in the two groups decreased by Degree I ~ IV, 62.5% (20/32) in study group and 52.8% (19/36) in control group. There was no significant difference between the two groups (p>0.05) (Table 3).

Discussion

Combined modality therapy for HCC, mainly consisting TACE, is an accepted therapy for unresectable HCC (Siperstein et al., 2001). However, the response rate of TACE is poor. The reason is due to a dual blood supply for hepatic tumor, the center of the tumor is mainly supplied by hepatic artery (Okusaka et al., 2000); while the activated marginal zone infiltrating the tumor and small nodules are supplied by portal , and it is further noted that the compensatory blood supply increased after 2 weeks of TACE (Lu et al., 1986). The periphery of the tumor mostly was the vigorous growth region. Residual cancer focus located under tumor capsule could grow rapidly and recur. The probability of portal vein blood supply increased, and there were comprehensive communicating branches between hepatic arterial and portal venous system, thus tumor could obtain blood supply through portal vein when hepatic artery being embolized, that is one of the reasons why simple TAE was ineffective (Okusaka et al., 2000).

On the other hand, 60~90% of HCC is complicated with portal vein tumor thrombus at the time of diagnosis. Portal vein tumor thrombus could be a cause of intrahepatic and extrahepatic metastasis, which is the main risk factor of unfavorable prognosis of HCC. Therefore, when PVE was employed following TAE (TAE+PVE) to treat patients with advanced HCC and complicated with portal vein tumor thrombus, tumor volume in 8 of 12 patients reduced for more than 50% and no PD was documented (Yu et al., 1996). After that, TAE+PVE was administrated in 105 patients with recurrent hepatic cancer, achieving a response rate of 57.2%, in which 68.8% of portal vein tumor thrombus vanished or decreased (Mao et al., 2002); the tumor necrosis rate was 73.7%; and the 1-, 2-and 3-year survival rates were 95.6%, 59.6% and 39.1% respectively (Mao et al., 2002). Therefore, theoretically, TAE+PVE is an ideal therapy for treating patients with unresectable advanced hepatic cancer (Pan et al., 2001). We also delivered TAE+PVE to 25 patients with PHC, 16 presented effective (Cui et al., 2004); the reduction rate of portal vein tumor thrombus was 66.7% and the 1-year survival rate was 72% (Cui et al., 2004). But the survival rate is still not satisfactory. Therefore, how to maximize the treatment efficacy and not to produce excessive side effects is still a clinical concern.

In recent years, HIFU is widely recommended as a non-invasive cancer treatment modality with satisfactory results (O'Neill et al., 2010). Preclinical experiments demonstrated the safety, efficacy and clinical feasibility of HIFU in the treatment of HCC (Cheung et al., 2012). HIFU is a technique by focusing low-energy ultrasound on tumor in vivo, making the temperature of treatment area rises to 65~100°C in 0.5~1.0s. Clinical studies suggested that HIFU+TACE therapy for hepatic cancer could greatly enhance the therapeutic effect (Zhang et al., 2009). In clinical studies, it is reported that TACE+PVE was firstly used in treating HCC (Zhang et al., 2009). This is because deposition of iodized oil had positioning function, and also increase the acoustic impedance difference of tumor area and improves the sound absorption coefficient, and having a synergistic effect on thermal effect of HIFU, accordingly significantly improved the thermal effect in HIFU treatment. Jin used HIFU+TAE to treat 124 patients with advanced hepatic cancer (Jin et al.,2003). Median survival time was 11.3 months; 6-month and 1-year survival rate were 80.4% and 42.9% respectively, while single TACE group were 13.2% and 0, and the difference between the two groups was statistically significant. Our study suggested that when HIFU was used after TACE +PVE, the effective rate was 72%, which is significantly higher than 44.4% in control group. In l0 patients with portal vein tumor thrombus, disease of 7 patients significantly decreased or vanished, and AFP value obviously decreased. During the follow-up, it was found that 1-, 2- and 3-year survival rates were 56.3%, 18.8%and 9.3% respectively, while 30.6%, 5.6% and 0 in control group. Furthermore, compared with control group, the disease control time was elongated, and the quality of life was significantly improved. In conclusion, our study indicated that TACE+PVE+HIFU therapy is associated with improved local tumor response rate, quality of life and extended survival time, with tolerable treatment-related side effects; thus could be considered for the treatment of advanced HCC.

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