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Original Article

Survival analysis of sorafenib combined with TACE in hepatocellular carcinoma patients

Jingqin Cao, Defen Zhang, Yingchun Zhang, Yanxiao Yue, Huaizhuang Cai, Jie Zhang, Zuoxiang Wang

Department of Interventional Radiology, Jining No.1 People's Hospital, Jining 272000, Shandong, China

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Abstract: Objective: To investigate the efficacy of transcatheter arterial chemoembolization (TACE) combined with sorafenib in the treatment of patients with hepatocellular carcinoma (HCC). Methods: A total of 100 patients with HCC admitted to our hospital were enrolled. 50 were assigned to the joint group for interventional therapy of sorafenib combined with TACE and another 50 were assigned to the single TACE group given TACE only. RECIST (Response Evaluation Criteria in Solid Tumors) was applied for evaluation of therapeutic efficiency, clinical benefit rate (CBR) and rate of adverse reaction. Overall survival (OS) and time to tumor progression (TTP) were analyzed. Results: After treatment, the CBR in the joint group was 66%, higher than that of 48.0% in the single TACE group ($P < 0.05$). The OS of joint group was notably superior to that of single TACE group ($X^2 = 7.441$, $P = 0.006$). TTP in the joint group significantly overtopped that in the single TACE group ($X^2 = 10.437$, $P = 0.001$). In terms of adverse reactions, the incidences of skin disease including pruritus, rash and alopecia, etc. in the joint group were remarkably higher than the those in the single TACE group ($P < 0.05$); little difference was observed with respect to adverse reactions involving the hands or feet between the two groups ($P > 0.05$); the incidences of diarrhea, loss of appetite, abdominal pain, fatigue, and hypertension in the joint group were significantly higher than those in the single TACE group ($P < 0.05$); however, fewer cases developed with nausea and vomiting, fever, myelosuppression or gastrointestinal bleeding in the joint group ($P < 0.05$); there was no significant difference in hepatic dysfunction between the two groups ($P > 0.05$). Conclusion: Sorafenib combined with TACE in the treatment of hepatocellular carcinoma may effectively lengthen the survival time and stabilize progression, and reduce the tolerance to adverse reactions, which is of importance in clinical practices.

Keywords: Sorafenib, interventional therapy, TACE, hepatocellular carcinoma

Introduction

Even occurred, latent hepatocellular carcinoma in the early stage hardly shows any early symptoms. When patients found the sign of it, they may have come near the middle and advanced stage. At present, hepatocellular carcinoma ranks the sixth among malignant tumors regarding its incidence. Limited to female patients only, it ranks the seventh by incidence and the sixth by mortality. Statistics reported that worldwide there were about 750,000 new cases of hepatic carcinoma and approximately 700,000 cases died of hepatic carcinoma in 2008. China now holds about 55% of global patients with hepatic carcinoma and 53% of annual hepatic carcinoma deaths over the world [1].

For early hepatic carcinoma, which is latent and if found shall be treated with excision, and most have developed into the middle and late stage at diagnosis. In this connection, TACE, as an important non-surgical therapy for the treatment of patients with advanced hepatic carcinoma, has shown the superior therapeutic effects, although most patients after treatment may be accompanied by fever or other clinical complications, and are facing risks of relapse, poor long-term effect and/or hepatic injury, etc. The fever occurred after TACE is mainly caused by ischemic necrosis of tissues due to embolism. As the ischemic necrosis aggravates, much more severe inflammatory reactions appear and increase the risks of fever [2].

Sorafenib, also known as Nexaudio-videoar, is classified as an oral multi-kinase inhibitor that

acts as a dual antibody against tumors. Clinical practices proved the ability of Sorafenib in elevating the survival rate of patients with hepatic carcinoma. It has been one of the more widely used drugs worldwide. For hepatic carcinoma, transcatheter arterial chemoembolization combined with Huaier Granule can effectively improve the therapeutic effect [3]. In view of this, HCC patients were enrolled for retrospective analysis of combined treatment with Sorafenib and TACE.

Material and methods

Material

A total of 100 patients (78 males and 22 females, aged 23-82 years) with hepatocellular carcinoma admitted to our hospital for TACE during December 2011-December 2017 were enrolled and divided into single TACE group (n = 50) and joint group (n = 50). Patients in single TACE group were given TACE alone, while patients in joint group were given sorafenib combined with TACE. Exclusion criteria: A subject who (1) is pregnant or in lactation period; or (2) has been attacked by active hemorrhagic gastric ulcer or gastrointestinal bleeding over the last 30 days; or (3) has congestive heart-failure of NYHA 2 or above, symptomatic coronary artery disease or arrhythmia requiring treatment with drugs other than β-blockers or digoxin; or (4) has severe active clinical infection, except HBV and HCV; or (5) had received sorafenib and despite the treatment of hypertension has systolic blood pressure > 150 mm Hg or diastolic blood pressure > 90 mm Hg, together with hepatic encephalopathy [5]; or (6) has a history of heart disease, active bleeding, AIDS, contraindication of oral drugs, or recent major surgery. Inclusion criteria: The two groups of subjects were diagnosed with hepatocellular carcinoma by biopsy in line with the diagnostic criteria for hepatic carcinoma; with BCLC-C and Child-Pugh A/B; and showed little differences in gender, age, education, tumor size, etc. ($P > 0.05$) but comparable instead. This study has been approved by the Ethics Committee of Jining No.1 People's Hospital. All study participants provided written informed consent before participating in the study.

Methods

TACE treatment: The two groups of patients were examined by abdominal CT or MRI and blood routine for hepatic function. For the TACE treatment, the dose of lipiodol and drugs used were determined by tumor size. After TACE, the two groups of patients were managed with conventional nursing for anti-infection, hepatic protection and pain relief. TACE could be repeated with an interval of 45 days according to the patient's condition.

Sorafenib combined with TACE: Sorafenib (200 mg/2 tablets once, twice a day) was given on the 3rd to 7th day after TACE in the joint group. Once the adverse reactions were relieved, drugs were administered at the original dose with the original interval in light of the patient's condition.

Outcome measures

Therapeutic efficiency: Tumor size was measured and curative effects were split into complete remission (CR), partial remission (PR), and stable disease (SD), and progressive disease (PD) were determined based on RESCIST. Clinical benefit rate (CBR) was calculated as CBR = CR + PR + SD. Time to tumor progression (TTP) was defined as the period from the start of treatment to tumour progression. Overall survival (OS) refers to the period of time from the start of treatment to death or the last follow-up (follow-up was organized every 6 to 8 weeks after surgery until death). Adverse reactions were assessed according to the American National Cancer Institute Common Terminology Criteria for Adverse Events, version 3 (NCI-CTCAE 3.0) [4].

Statistics

SPSS 13.0 software package was used for statistical analysis. Enumeration data was subject to χ^2 test. OS, TTP and curves between the two groups were plotted using Kaplan-Meier. $P < 0.05$ suggested a statistically significant difference.

Results

Evaluation of therapeutic efficiency

After treatment, PR and SD in joint group were significantly higher than those in single TACE group ($P < 0.05$); PD in joint group was smaller compared with the single TACE group ($P < 0.05$); little difference was found in CR between the two groups ($P > 0.05$) (**Table 1**).

Table 1. Curative effects compared between the two groups of patients

Group	n	n				CBR (%)
		CR	PR	SD	PD	
Joint group	50	0	4	29	17	66.0
Single TACE group	50	0	0	22	26	48.0
P		1.000	0.014	0.022	0.035	0.047

Table 2. OS and TTP comparison between the two groups (month)

Group	n	OS		TTP	
		M	95% CI	M	95% CI
Joint group	50	30	14.9~27.1	10	8.7~13.3
Single TACE group	50	18	6.4~13.6	5	3.9~8.1
X^2		7.441		10.437	
P		0.006		0.001	

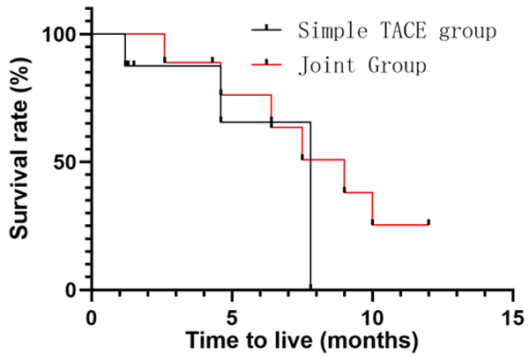

Figure 1. Survival rate in the two groups of patients. The overall survival of joint group was significantly higher than that of single TACE group, except that at 13-15 months, the overall survivals between the two groups were not notably different (P = 1.001).

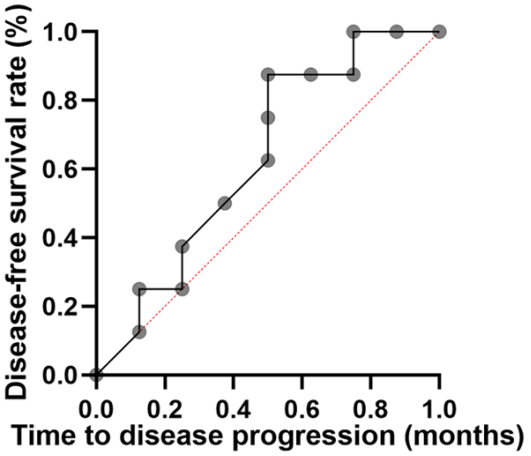

Figure 2. Disease-free survival rate with TTP in the two groups of patients. At 13-15 months, the disease-free survival rate with TTP was coincident between the two groups. Excepting that, the TTP in joint group was statistically lower than that in single TACE group (P = 0.038).

Survival evaluation

Kaplan-Meier analysis showed that 30 of 50 patients survived in the joint group as of the end of follow-up, with a survival rate of 60.0%; 18 of 50 patients survived in the single TACE group resulting in a survival rate of 36.0%. The difference was statistically significant (X^2 = 7.441, P = 0.006). TTP from the joint group was notably higher than that from the single TACE group (X^2 = 10.437, P = 0.001) (**Table 2**). OS and TTP survival curves in both groups are shown in **Figures 1** and **2**.

Adverse reactions

In terms of adverse reactions, the incidence of skin disease included pruritus (58.0%), rash (20.0%) and alopecia (16.0%), etc. in the joint group, of them all were remarkably higher than the counterparts in the single TACE group (0.00%, 1.00%, & 14.00%) (P < 0.05); little difference was reported with respect to adverse reactions involving the hands or feet between the two groups (P > 0.05); the incidence of diarrhea, loss of appetite, abdominal pain, fatigue, and hypertension among adverse gastrointestinal diseases in the joint group was significantly higher than those in the single TACE group (P < 0.05) (**Table 3**, **Figure 3**).

Discussion

Hepatocellular carcinoma has been one of the malignant tumors of high incidence in China recently [5, 6]. MRI is now mostly used for detection of hepatocellular carcinoma in clinical practices by testing viable tissues in a state of hydrone diffusion, which directly reflects the characteristics of lesions [7, 8]. As mentioned earlier, early hepatic carcinoma is not easy to detect and most developed into the middle or advanced stage at diagnosis [9, 10]. TACE is mainly used for the treatment of advanced hepatic carcinoma and shows good therapeutic effects, although patients may face with risks

Table 3. Adverse reactions compared in both groups (n, %)

Adverse reaction	Joint gorup (n = 50)	Single TACE group (n = 50)	X^2	P
Skin diseases				
Pruritus	29 (58.0)	3 (6.00)	35.163	0.000
Rash	10 (20.0)	0 (0.00)	10.459	0.002
Alopecia	8 (16.0)	5 (1.00)	0.707	0.398
Hands and feet events	7 (14.0)	7 (14.0)	0.000	1.000
Gastrointestinal reactions				
Diarrhea	19 (38.0)	7 (14.0)	6.045	0.011
Loss of appetite	24 (48.0)	21 (42.0)	0.715	0.431
Nausea and vomiting	17 (34.0)	19 (38.0)	0.167	0.714
Fever	20 (40.0)	21 (42.0)	0.046	0.831
Stomachache	13 (26.0)	9 (18.0)	0.970	0.325
Fatigue	21 (42.0)	17 (34.0)	0.421	0.517
Hypertension	8 (16.0)	4 (8.00)	2.600	0.104
Gastrointestinal bleeding	4 (8.00)	5 (1.00)	0.135	0.743
Hepatic dysfunction	9 (18.0)	9 (18.0)	0.000	1.000
Myelosuppression	5 (1.00)	6 (12.0)	0.205	0.679

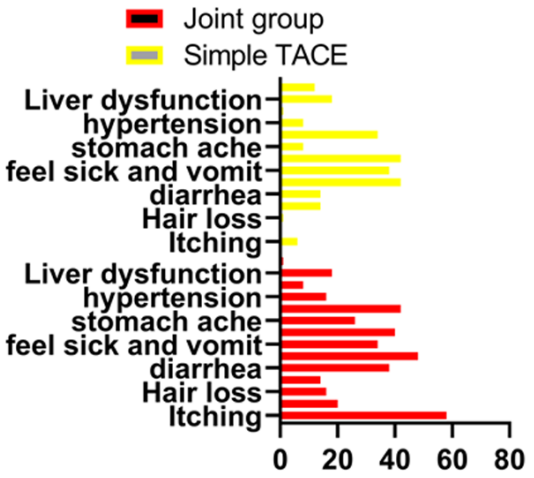

Figure 3. Incidence of adverse reactions in the two groups. The incidence of skin disease and gastrointestinal reaction in joint group was remarkably higher than that in single TACE group (P = 0.014); whilst the bone marrow transplantation in joint group was less compared with the single TACE group (P = 0.136), suggesting that such a combination could increase the occurrence of adverse reactions, but the survival was superior though.

of recurrence and poor long-term effect [11, 12]. However, TACE promotes tumor necrosis by reducing blood perfusion into tumor tissues. Despite this, TACE alone is less effective and requires repeated treatments before offering excellent efficiency [13, 14]. In some hepatic carcinoma, the fasciculate feeding artery or insufficient blood supply for arteries leads to unqualified intralesional precipitation of iodide and chemotherapeutic drugs, lowering the positive tumor necrosis. As required, repeated application of TACE exerts damage to liver function and directly affects the survival of patients [15, 16].

Sorafenib has a significant effect in the treatment of hepatocellular carcinoma and is widely used in clinical practice. It is superior to other regimens in promoting tumor necrosis and reducing recurrence so as to improving the survival time of patients [17, 18]. Sorafenib is considered to be a multi-kinase inhibitor [19, 20]. Up till now, the clinical treatment of hepatocellular carcinoma mostly refers to chemical drugs combined with TACE. Combination of Chinese and Western therapy has not yet been proved [21, 22]. Tumors gain nutrition from human blood. The disconnection from nutritional supplies inhibits its growth. This is exactly how TACE works. By TACE, chemotherapeutic drugs and embolic agents are injected into the feeding arteries connecting hepatic carcinoma and retained in the blood vessels so as to act for a long period of time in inhibiting the growth of tumor cells [23, 24]. Takahito et al. found that the incidence of adverse reactions in joint group was significantly higher than that in single TACE group; this could be explained by that both regimens gave rise to adverse reactions [25]. In this study, the clinical effects in joint group were superior to those in single TACE group. So were the overall survival and time to progression.

In summary, sorafenib combined with Huaier Granule in the treatment of hepatocellular carcinoma offered the advantages of each method, and achieved better condition of stable disease and survival. Furthermore, the adverse reactions caused by sorafenib are tolerable. Such a combination may provide a good reference to the treatment of hepatocellular carcinoma.

Disclosure of conflict of interest

None.

Address correspondence to: Zuoxiang Wang, Department of Interventional Radiology, Jining No.1 People's Hospital, No.6, Jiankang Road, Jining 272000, Shandong, China. Tel: +86-0537-2253-492; E-mail: zuoxiangwang11@163.com

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