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Original Article

Unresectable hepatocellular carcinoma treated with transarterial chemoembolization: clinical data from a single teaching hospital

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Abstract: The aim of this study is to evaluate the survival rates of patients with unresectable hepatocellular carcinoma (HCC) following transarterial chemoembolization (TACE) performed in a single teaching hospital. This study retrospectively assessed the electronic medical records of 217 patients in whom HCC was newly diagnosed from January 2009 to February 2013 at a single medical center. Hepatic artery infusion chemotherapy was performed using one drug or combinations of oxaliplatin, fluorouracil and doxorubicin. The primary endpoint of the study was overall survival (OS). Survival rates were calculated using Kaplan-Meier method. A total of 217 HCC patients (173 men and 44 women; mean age, 56.3 years; age range, 36.1-84.3 years) were treated with TACE in a single center. The overall survival rates at 1 and 2 years were 64% and 40%, respectively. The overall median survival time from the start of TACE treatment was 13 months. Our results indicated that TACE is an effective minimally invasive therapy option for palliative treatment of HCC patients.

Keywords: Chemoembolization, embolization, hepatocellular carcinoma, transarterial chemoembolization

Introduction

Liver cancer in men is the fifth most frequently diagnosed cancer worldwide but the second most frequent cause of cancer death. In women, it is the seventh most commonly diagnosed cancer and the sixth leading cause of cancer death. Half of these cases and deaths were estimated to occur in China [1]. Among primary liver cancers, hepatocellular carcinoma (HCC) represents the major histological subtype, accounting for 70% to 85% of the total liver cancer burden worldwide [1]. However, most HCC patients are unresectable at diagnosis because of multicentricity, large tumor size or a poor hepatic functional reserve due to preexisting cirrhosis, or they are not transplantable because of an advanced tumor stage or severe comorbidity [2]. Therefore, transarterial chemoembolization (TACE) seems to be more important as a treatment strategy [3].

TACE is the current standard of care for patients presenting with multinodular HCC and relatively preserved liver function, absence of cancer-related symptoms, and no evidence of vascular invasion or extrahepatic spread [4-6]. The aim of the current study was to investigate survival rates of patients with HCC undergoing TACE.

Patients and methods

Patients

The institutional ethical committee approved the current retrospective study. A written informed consent was obtained for all patients. We reviewed the electronic medical records of consecutive patients in whom HCC was newly diagnosed from January 2009 to February 2013 at Yinzhou People's Hospital Affiliated to Ningbo University School of Medicine (**Table 1**). The diagnosis of HCC was mainly based on recommendations of the American Association for the Study of Liver Diseases [7]. All patients underwent blood investigations, which included complete blood count, liver function tests, and tests for viral markers of hepatitis B and C infec-

Table 1. Characteristics of the patients with unresectable hepatocellular carcinoma treated with transarterial chemoembolization (TACE)

Variables	n=217	
Demography	Age (years, mean ± SD)	56.3 ± 11.7
	Male (n/%)	173/79.7
	Female (n/%)	44/20.3
Liver function	ALT (IU/L)	
	<40 (n/%)	23/10.6
	>40 (n/%)	194/89.4
	AST (IU/L)	
	<40 (n/%)	28/12.9
	>40 (n/%)	189/87.1
Tumor maker	AFP (ng/ml)	
	<20 (n/%)	37/17.1
	21-200 (n/%)	59/27.2
	>200 (n/%)	121/55.7
Etiology of cirrhosis	HBV (n/%)	176/81.1
	HCV (n/%)	28/12.9
	Others (n/%)	13/6.0
BCLC staging	B (n/%)	165/76.0
	C (n/%)	52/24.0
Child's score	A (n/%)	191/88.0
	B (n/%)	26/12.0
Number of masses	Single (n/%)	138/63.6
	Multiple (n/%)	79/36.4
Post-TACE complications	Postembolization syndrome (n/%)	28/12.9
	Hepatic failure (n/%)	3/3.7
Postinterventional evaluation	SD (n/%)	35/16.1
	CR (n/%)	78/35.9
	PR (n/%)	67/30.9
	PD (n/%)	37/17.1
Overall survival rate	1-year (%)	64
	2-year (%)	40

Abbreviations: HBV, hepatitis B virus infection; HCV, hepatitis C virus infection; AST, aspartate aminotransferase; ALT, aspartate aminotransferase; AFP, alpha-fetoprotein; BCLC staging, barcelona clinic liver cancer staging; TACE, transarterial chemoembolization; SD, stable disease; CR, complete response; PR, partial response; PD, disease progression.

tion. Serum alpha-fetoprotein (AFP) was estimated using a particle enzyme immunoassay (Axsym System; Abbott Laboratories, Abbot Park, Illinois, USA; normal value <20 ng/ml). Upper gastrointestinal endoscopy was done in each case to detect the presence of esophageal varices. Patients with underlying cirrhosis were classified into Child's A, B or C based on the Child-Pugh classification [8]. Staging of HCC was done based on the Barcelona Clinic Liver Cancer (BCLC) staging protocol [9]. TACE was offered to BCLC-B/C HCC patients who fulfilled the following inclusion criteria: patients with associated Child's A or B cirrhosis, normal main portal vein, less than 50% involvement of liver by HCC, and patients willing for therapy and follow-up. Patients were excluded from this study if they (a) had decompensated liver function classified as Child-Pugh class C disease; (b) had previously received intraarterial chemoinfusion; (c) had previously received radiofrequency ablation; (d) had previously received percutaneous ethanol injection; (e) had previously received laser-induced thermotherapy; (f) had serious medical comorbidities; (g) had or previously had malignant tumors in addition to HCC; (h) had undergone organ transplantation; and (i) had extra hepatic disease; coagulopathy; biliary obstruction; comorbid illness like coronary artery disease, congestive heart failure, chronic renal failure, etc.; and a previous history of encephalopathy/upper gastrointestinal bleed in the last 6 months.

TACE procedure

Prophylactic antibiotics were given to all patients: cefazolin 1 g intravenously (IV) every 8 h (three doses) and metronidazole 500 mg IV every 6 h (four doses). All patients also received diphenhydramine 50 mg IV, ondansetron 8 mg IV every 8 h (three doses) and dexamethasone 8 mg IV every 8 h (three doses). Fentanyl 50 μg to 150 μg IV or morphine 5 mg to 10 mg IV, and midazolam 1 mg to 5 mg IV were used to achieve moderate sedation.

Digital subtraction angiography (DSA; Multistar, Siemens, Erlangen, Germany) was performed in all patients immediately before TACE. All

TACE followed a standard protocol and was performed by a single experienced interventionist with more than 10 years of experience in interventional radiology. TACE was performed using the Seldinger technique [10]. After the introduction of a 5 French sheath into the femoral artery, visceral angiography was carried out to assess the arterial blood supply to the liver and to confirm patency of the portal vein. Then right and left hepatic angiography was performed, followed by selective catheterization of the arteries feeding the tumors. Depending on size, location, and arterial supply to the tumor, the tip of the catheter was advanced further into the segmental arteries.

The chemotherapeutic suspension consisted of one drug or combinations of oxaliplatin (100-200 mg, Hengrui Medicine Co., Ltd., Jiangsu, China) and fluorouracil (0.5-1.0 g, Xudong Haipu Pharmaceutical Co., Ltd., Shanghai, China). All drug suspensions were diluted in 50 mL overall volume syringes using normal saline (0.9% NaCl). After that, chemoembolization was performed using doxorubicin (30-50 mg, Adriblastine; Pfizer, Nerviano, Italy) mixed with a maximum of 20 mL iodized oil (lipiodol, Lipiodol Ultra-Fluide; Andre Guerbet Laboratories, Aulnay-Sous-Bois, France). The administration of lipiodol chemotherapy was followed by embolization with hand cut gelatin sponge particles (Spongostan Standard; Johnson and Johnson Medical Limited, Gargrave, Skipton, UK). Embolization was always performed. When flow was significantly reduced, embolization was started few minutes later to allow flow restoration. The amount of administered Lipiodol and anticancer drug used for TACE was decided on the basis of number, location and diameter of lesions. After embolization, devascularization was confirmed with additional angiography of the hepatic artery.

Data collection and follow-up

The clinical, laboratory, and radiologic records of all patients were retrospectively reviewed (**Table 1**). The results of all 217 patients (173 men, 44 women) with unresectable HCC were analyzed. Follow-up cross-sectional imaging (contrast-enhanced CT or MRI) was performed one month after treatment. Further treatments were based on clinical evaluation, laboratory values and imaging response. Patients with progressive disease underwent repeat treatments with the same modality. Patients with stable disease were followed with cross-sectional imaging every 3 months. Tumor response to TACE was evaluated according to World Health Organization (WHO) criteria [7]. Liver function tests were checked in all patients every three months in order to evaluate hepatic functional reserve. The endpoint of the study was survival. Overall survival was calculated from the date of commencement of TACE to the date of death for any cause or last follow-up.

Statistical analysis

Descriptive statistics (mean ± SD) were provided when appropriate. Survival was analyzed by using the Kaplan-Meier method for the whole patient population and compared by using the log-rank test. All statistical analyses were performed with software (SPSS 16.0 statistical package; SPSS, Chicago, Ill). $P<0.05$ was considered indicative of a statistically significant difference.

Results

A total of 217 patients with unresectable HCC were eligible for TACE. The patients were successfully subjected to a total of 556 sessions (2.5 ± 1.13) of TACE. The clinical profile of the study population is depicted in **Table 1**. The 217 patients (173 males, 44 females) had a mean age of 56.3 ± 11.7 years (range: 36.1-84.3 years). Hepatitis B virus (HBV) infection was the most common etiological factor of HCC, seen in 176 (81.1%) patients. Hepatitis C virus (HCV) infection was the second common etiological factor of HCC, seen in 28 (12.9%) patients, and others were seen in 13 (6.0%) patients. BCLC B patients were 165 (76.0%), and BCLC C patients were 52 (24.0%). The mean tumor size was 6.3 ± 2.35 cm (range: 1.4-12.6 cm).

The procedure of TACE was well tolerated by all our patients. No complications were encountered during the procedure and the postprocedure complications were mild. Postembolization syndrome was the most common complication in 28 patients (12.9%), which consisted of pain abdomen, fever, nausea, and vomiting. Hepatic failure in 8 patients (3.7%) was also encountered.

The postinterventional evaluation after TACE revealed an SD in 16.1% (35/217) of patients, a CR in 35.9% (78/217) of patients, a PR in 30.9% (67/217) of patients, and a PD in 17.1% (37/217) according to the WHO criteria.

The median duration of follow-up was 12.3 months (range: 1-33 months). According to the Kaplan-Meier method median survival time from the start of TACE was 13 months. Results of treatment starting from the first TACE indicated that the overall survival rates at 1 and 2 years were 64% and 40%, respectively (**Table 1**).

Discussion

Patients with advanced HCC are a heterogeneous group in terms of clinical status, residual liver function, and tumor characteristics. The developing world has a peculiar epidemiological variation in terms of etiology and the stage of HCC at diagnosis; more than 80% of the HCC occurs in Asia and Africa [1]. Surgery as the usual treatment modality is a therapeutic option in only 15% of HCC cases because of the large size or multiplicity of the primary tumors or accompanying cirrhosis. TACE has been widely accepted as a mainly palliative approach to treat HCC in patients that are primarily no candidates for surgery [2, 11]. In a meta-analysis including 18 randomized controlled trials, Camma et al. reported a statistically significant improvement of survival or time to progression with TACE as compared with the control groups [12].

In this study, HBV infection emerged as the most common background causal factor for HCC. This is consistent with the observations of published studies from India [13], Korea [14], and China [15]. In contrast, in countries like Japan [16], France [17], and Italy [11], HCV related HCC is predominantly encountered.

Oxaliplatin, fluorouracil and doxorubicin are the common antitumor drugs used alone or in combination during TACE in China. No standardized protocol exists with regard to the choice of the chemotherapeutic agent, dosage, dilution, rate of injection, and optimal re-treatment strategy. Similarly, there is no standard choice for the embolizing agent to be used or its quantity. In the present study, we used a combination of oxaliplatin, fluorouracil, doxorubicin and lipiodol, followed by particulate embolization using gelatin sponge.

TACE is known to be a safe procedure with a low mortality rate and, further, the mortality has been decreasing over the last two decades (reportedly 10% in 1991, 1.1% in 1999, and 0.5% in 2006) [16, 18, 19]. We lost three patients one month after performing TACE due to hepatic failure, leading to a procedure-related mortality of 1.4%.

The survival rate and the local response in our study were encouraging. The overall survival rate at 1 and 2 years were 64% and 40%, respectively. The overall survival rate in our study compares well with many earlier studies from different countries [20-22]. Due to differences in the selection criteria, our study population probably had a larger tumor size and more advanced stage of disease.

In conclusion, TACE is a safe and efficacious palliative procedure for palliative treatment of unresectable HCC patients. In China, the majority of patients with HCC have advanced disease at presentation. Despite the presence of large-sized tumors in our study population, TACE showed favorable overall survival rates comparable with those reported by other authors. With further advances in medicine, patients with unresectable HCC will be able to enjoy better survival.

Conflict of interest

None.

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References

[1] Jemal A, Bray F, Center MM, Ferlay J, Ward E and Forman D. Global cancer statistics. CA Cancer J Clin 2011; 61: 69-90.
[2] Forner A, Llovet JM and Bruix J. Hepatocellular carcinoma. Lancet 2012; 379: 1245-1255.
[3] Brown DB, Geschwind JF, Soulen MC, Millward SF and Sacks D. Society of Interventional Radi-

ology position statement on chemoembolization of hepatic malignancies. J Vasc Interv Radiol 2006; 17: 217-223.
[4] Llovet JM, Di Bisceglie AM, Bruix J, Kramer BS, Lencioni R, Zhu AX, Sherman M, Schwartz M, Lotze M, Talwalkar J, Gores GJ; Panel of Experts in HCC-Design Clinical Trials. Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst 2008; 100: 698-711.
[5] Bruix J, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology 2011; 53: 1020-1022.
[6] European Association For The Study Of The Liver and European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 56; 2012: 908-943.
[7] Bruix J, Sherman M; Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. Hepatology 2005; 42: 1208-1236.
[8] Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC and Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973; 60: 646-649.
[9] Cillo U, Vitale A, Grigoletto F, Farinati F, Brolese A, Zanus G, Neri D, Boccagni P, Srsen N, D'Amico F, Ciarleglio FA, Bridda A and D'Amico DF. Prospective validation of the Barcelona Clinic Liver Cancer staging system. J Hepatol 2006; 44: 723-731.
[10] Seldinger SI. Catheter replacement of the needle in percutaneous arteriography. A new technique. Acta Radiol Suppl (Stockholm) 2008; 434: 47-52.
[11] Caturelli E, Siena DA, Fusilli S, Villani MR, Schiavone G, Nardella M, Balzano S and Florio F. Transcatheter arterial chemoembolization for hepatocellular carcinoma in patients with cirrhosis: evaluation of damage to nontumorous liver tissue-long-term prospective study. Radiology 2000; 215: 123-128.
[12] Cammà C, Schepis F, Orlando A, Albanese M, Shahied L, Trevisani F, Andreone P, Craxì A and Cottone M. Transarterial chemoembolization for unresectable hepatocellular carcinoma: meta-analysis of randomized controlled trials. Radiology 2002; 224: 47-54.
[13] Sarin SK, Thakur V, Guptan RC, Saigal S, Malhotra V, Thyagarajan SP and Das BC. Profile of hepatocellular carcinoma in India: an insight into the possible etiologic associations. J Gastroenterol Hepatol 2001; 16: 666-673.
[14] Kang JY, Choi MS, Kim SJ, Kil JS, Lee JH, Koh KC, Paik SW and Yoo BC. Long-term outcome of preoperative transarterial chemoembolization and hepatic resection in patients with hepatocellular carcinoma. Korean J Hepatol 2010; 16: 383-388.
[15] Shi M, Chen JA, Lin XJ, Guo RP, Yuan YF, Chen MS, Zhang YQ and Li JQ. Transarterial chemoembolization as initial treatment for unresectable hepatocellular carcinoma in southern China. World J Gastroenterol 2010; 16: 264-269.
[16] Takayasu K, Arii S, Ikai I, Omata M, Okita K, Ichida T, Matsuyama Y, Nakanuma Y, Kojiro M, Makuuchi M, Yamaoka Y; Liver Cancer Study Group of Japan. Prospective cohort study of transarterial chemoembolization for unresectable hepatocellular carcinoma in 8510 patients. Gastroenterology 2006; 131: 461-469.
[17] A comparison of lipiodol chemoembolization and conservative treatment for unresectable hepatocellular carcinoma. Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire. N Engl J Med 1995; 332: 1256-1261.
[18] Vetter D, Wenger JJ, Bergier JM, Doffoel M and Bockel R. Transcatheter oily chemoembolization in the management of advanced hepatocellular carcinoma in cirrhosis: results of a Western comparative study in 60 patients. Hepatology 1991; 13: 427-433.
[19] Savastano S, Miotto D, Casarrubea G, Teso S, Chiesura-Corona M and Feltrin GP. Transcatheter arterial chemoembolization for hepatocellular carcinoma in patients with Child's grade A or B cirrhosis: a multivariate analysis of prognostic factors. J Clin Gastroenterol 1999; 28: 334-340.
[20] Miyayama S, Yamashiro M, Okuda M, Yoshie Y, Sugimori N, Igarashi S, Nakashima Y, Notsumata K, Toya D, Tanaka N, Mitsui T and Matsui O. Chemoembolization for the treatment of large hepatocellular carcinoma. J Vasc Interv Radiol 2010; 21: 1226-1234.
[21] Pelletier G, Ducreux M, Gay F, Luboinski M, Hagège H, Dao T, Van Steenbergen W, Buffet C, Rougier P, Adler M, Pignon JP and Roche A. Treatment of unresectable hepatocellular carcinoma with lipiodol chemoembolization: a multicenter randomized trial. Groupe CHC. J Hepatol 1998; 29: 129-134.
[22] Pelletier G, Roche A, Ink O, Anciaux ML, Derhy S, Rougier P, Lenoir C, Attali P and Etienne JP. A randomized trial of hepatic arterial chemoembolization in patients with unresectable hepatocellular carcinoma. J Hepatol 1990; 11: 181-184.