RESEARCH ARTICLE

Transcatheter Arterial Chemoembolization Combined with Interferon-α is Safe and Effective for Patients with Hepatocellular Carcinoma after Curative Resection

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Abstract

__Objectives:__ Intrahepatic recurrence is the major cause of death among patients with hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC) after curative surgical resection. Several approaches have been reported to decrease the recurrence rate. The objective of our study was to compare the clinical effects of transcatheter arterial chemoembolization (TACE) combined with interferon-alpha (IFN-α) therapy on recurrence after hepatic resection in patients with HBV-related HCC with that of TACE chemotherapy alone. __Methods:__ We retrospectively analyzed the data from 228 patients who were diagnosed with HBV-related HCC and underwent curative resection between January 2001 to December 2008. The patients were divided into TACE (n = 126) and TACE-IFN-α (n = 102) groups for postoperative chemotherapy. The TACE regimen consisted of 5-fluorouracil (5-FU), cisplatin (DDP) , and the emulsion mixed with mitomycin C (MMC) and lipiodol. The recurrence rates, disease-free survival (DFS), overall survival (OS), and risk of recurrence were evaluated. __Results:__ The clinicopathological parameters and adverse effects were similar between the 2 groups ($P > 0.05$). The median OS for the TACE-IFN-α group (36.3 months) was significantly longer than that of the TACE group (24.5 months, $P < 0.05$). The 3-and 5-year OS for the TACE-IFN-α group were significantly longer than those of the TACE group ($P < 0.05$) and the recurrence rate was significantly lower ($P < 0.05$). The TACE and IFN-α combination therapy, active hepatitis HBV infection, the number of tumor nodules, microvascular invasion, liver cirrhosis, and the BCLC stage were independent predictors of OS and DFS. __Conclusions:__ The use of the TACE and IFN-α combination chemotherapy after curative hepatic resection safely and effectively improves OS and decreases recurrence in patients with HBV-related HCC who are at high risk. Our findings can serve as a guide for the selection of postoperative adjuvant chemotherapy for patients with HBV-related HCC who are at high risk of recurrence.

Keywords: HCC - hepatitis B virus - TACE - interferon-α - combined treatment - overall survival - disease-free survival

Introduction

Hepatocellular carcinoma (HCC) is one of the most common causes of cancer-related deaths worldwide. In 2008, an estimated 748, 300 new liver cancer cases and 695 900 cancer-related deaths occurred worldwide (Jemal et al., 2011). Approximately 50% of these incident cases and deaths occurred in China, among which over 90% of the incident patients were chronically infected with the hepatitis B virus (HBV) (Ferlay et al., 2010). Hepatic resection is still a major curative treatment for patients with HCC (Fan et al., 2011). However, the long-term prognosis of HCC patients following hepatic resection is poor because of the high rate of recurrence. Previous studies have reported a 5-year cumulative recurrence rate of 70% to 80% for HCC (Fina et al., 2012).

Adjuvant treatments have been used in an attempt to decrease the recurrence of HCC after curative surgical resection (Lin et al., 2012). Transcatheter arterial chemoembolization (TACE) has demonstrated a significant therapeutic benefit in patients with moderate to advanced inoperable HCC (Li et al., 2013). However, certain previous studies have shown that adjuvant TACE does not improve overall survival (OS) and disease-free survival (DFS) in HCC patients. Therefore, the effect of TACE on the long-term prognosis of HCC patients following

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curative resection remains unclear (Choi et al., 2009).

Interferon-alpha (IFN-α) belongs to the type I interferon family of cytokines, a class of proteins that were originally identified due to their antiviral properties. However, IFN-α also exhibits antitumor activity, which includes the direct inhibition of tumor cell proliferation through the induction of proapoptotic genes, the inhibition tumor-related angiogenesis, and immunomodulatory effects that enhance the immunogenicity of tumor cells and improve liver function (Herzer et al., 2009; Lai et al., 2013; Jian et al., 2014; Lamm et al., 2014).

Although recent studies have shown that IFN-α therapy improves the prognosis of HCC patients, the efficacy of TACE combined with IFN-α for adjuvant chemotherapy following hepatic resection is unclear. The aim of our current study was to determine the efficacy of TACE and IFN-α combination chemotherapy in patients with HBV-related HCC based on their long-term outcomes. We also sought to identify prognostic factors associated with OS and DFS in patients with HBV-related HCC.

Materials and Methods

Study design

Our study was approved by the Institutional Review Board and the Ethics Committee of Hunan Province Cancer Hospital and the Second Xiangya Hospital of Central South University (Changsha, Hunan, China). Informed consent was obtained from all of the patients included in our study. We retrospectively reviewed the medical records of 3090 patients who received a histopathologically confirmed diagnosis of HCC between January 2001 and December 2008 at the department of general surgery at Hunan Province Cancer Hospital and the Second Xiangya Hospital of Central South University. 1640 patients were at Hunan Province Cancer Hospital, and 1450 patients were at the Second Xiangya Hospital of Central South University. 2760 patients were HBV-related HCC. Finally, a total 228 patients were enrolled into the analyses, and 176 patients were at Hunan Province Cancer Hospital, and 52 patients were at the Second Xiangya Hospital of Central South University. The inclusion criteria were as follows: (1) Underwent curative resection for HBV-related HCC, with the complete resection of all tumor nodules and histologically confirmed cancer-free surgical margins ≤ 1.0 cm; (2) no cancerous invasion of the main trunk or major bifurcations of the portal vein, the hepatic veins, or the bile duct; (3) no distant extrahepatic metastases; (4) tumor size > 5 cm; (5) ≤ 3 satellite tumor nodule; (6) postoperative serum level of α-fetoprotein (AFP) < 20 ng/mL after resection; and (7) an HBV DNA level > 10^5 copies/mL.

Surgical resection

Each patient received curative hepatectomy according to the anatomical principles of resection whenever possible. Intraoperative ultrasonography (US) was used to identify any occult tumors that were not detected preoperatively, and to confirm the relationship between the tumor and the vasculobiliary structures. Parenchymal dissection was performed using ultrasonic dissectors.

Postoperative adjuvant chemotherapy

Adjuvant TACE was performed 1-2 months in 228 patients with high risk of recurrence after hepatectomy. A vascular catheter was inserted through the femoral artery using the Seldinger technique, and hepatic angiography was performed. The catheter's tip was inserted selectively into the left, right hepatic artery or the branch artery when technically possible. The preventive or therapeutic chemoembolization was done depending on the patients with or without tumor stain in the remnant liver, respectively. The regimen consisted of 5-fluorouracil (5-FU) 0.75 g, cisplatin (DDP) 60 mg, and the emulsion mixed with mitomycin C (MMC) 16 mg and lipiodol 5 ml. It was injected slowly through the catheter. TACE was repeated every two to four months and no more than three times for each patient. The interval and times of repeated TACE depended on the response of the patients. The lipiodol was used in all procedures and followed up by computed tomography (CT) scan of the liver remnant 1 month later to document that there was no local recurrence. If there was early local recurrence, it would be shown as dense foci of lipiodol uptake, or as enhancing nodule not present in the preoperative CT.

Each patient received a subcutaneous injection of 3×10^6 U of IFN-α (Sinogen, Kexing Bioproducts, Shenzhen, China) 2 times per week for 2 weeks, followed by the injection of 5×10^6 U of IFN-α 3 times a week for 18 months. If recurrence occurred, the IFN-α treatment was terminated. The HCC patients were informed to perform TACE-IFN-α (best options) and TACE because of high risk of recurrenc after hepatectomy. However, 126 patients refused IFN-α treatment (control group) because of the costs, and TACE was performed only.

Study variables

All of the demographic and clinicopathological data had been previously recorded in a computer database. The HCC diagnosis was reconfirmed for all of the patients based on the practice guidelines of the American Association for the Study of Liver Disease (Chun et al., 2011). Every 3 months post treatment, the HBV DNA and AFP levels were determined, and computed tomography (CT) and US imaging or a magnetic resonance imaging (MRI) were performed. High-resolution contrast-enhanced CT and/or MRI were performed to confirm the presence of recurrent lesions. We defined OS of patients as the interval between the date of the HCC resection and the date of their death or the date of the last follow-up examination preceding their death. Patients who survived to the end of follow-up period were censored. Disease-free survival (DFS) was calculated from the date of the HCC resection to the date of the first radiological findings of recurrence. Patients that died with no sign of recurrence were censored.

Statistical analysis

The intergroup differences in the categorical variables were analyzed using a chi-squared analysis and a 2-tailed Fisher exact test. The median and range of the continuous variables were calculated. We used the single nearest-neighbor matching method without replacement (a single participant could not be selected multiple times) to match

Table 1. Clinicopathological Characteristics of Patients in the TACE-IFN-α and TACE Groups

Variables	TACE-IFN-α (n = 102)	TACE (n = 126)	P
Men/women (%)	91 (89.2)/11 (10.8)	113 (89.7)/13 (10.3)	0.909
Age (y)*	53 (20-79)	52 (19-78)	0.607
Hepatitis status, active/ non-active (%)	68 (66.7)/34 (33.4)	86 (68.3)/40 (31.7)	0.799
Liver cirrhosis (%)	87 (85.3)/15 (14.7)	108 (85.7)/18 (14.3)	0.929
Presence/absence tumor capsule (%)	57 (55.9)/45 (44.1)	70 (54.8)/56 (45.2)	0.961
1/≥ 2 tumor nodules (%)	56 (54.9)/46 (45.1)	69 (54.8)/57 (45.2)	0.893
Microvascular invasion (%)	77 (75.5)/25 (24.5)	93 (73.8)/33 (26.2)	0.772
Serum albumin (g/L)*	40 (29-47)	40 (24-51)	0.418
Total bilirubin (μmol/L)*	16.5 (5.8-93.8)	17.1 (10.6-104.5)	0.381
Prothrombin time (s)*	11.9 (9.4-17.4)	13.2 (8.1-18.5)	0.474
Platelet count (10^9/L)*	176.4 (63.3-269.0)	179.2 (59.3-294.0)	0.092
Serum ALT (U/L)*	49 (12–297)	51 (9–286)	0.782
Serum AFP > 400 ng/mL/≤ 400 ng/mL (%)	47 (46.1)/ 55 (53.9)	51 (40.5)/ 75 (59.5)	0.396
HBV DNA level (10^5 copies/mL)*	6.98 (0.7-7.9)	7.11 (1.2-8.1)	0.115
Platelet count (10^9/L)*	214.0 (69.0–508.0)	208.0 (57.0–630.0)	0.705
BCLC stage B/C (%)	45 (44.1)/57 (55.9)	58 (46.0)/68 (54.0)	0.773

TACE, transarterial chemoembolization; IFN-α, interferon alpha; ALT, alanine aminotransferase; AFP, α-fetoprotein; HBV, hepatitis B virus; BCLC, Barcelona clinical liver Cancer; *Reported as the median (range)

patients in the TACE group to patients in the TACE-IFN-α group using the psmatch2 command in the Stata statistical software (Stata Corp, College Station, TX, USA) (Kurth et al., 2006). Intergroup differences in the continuous variables were analyzed using the Mann-Whitney U test. Survival curves were constructed using the Kaplan-Meier method, and the significance of the intergroup differences in OS and DFS were evaluated using the log-rank test. Multivariate analyses of OS and DFS were performed using Cox proportional hazards models to estimate the adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). With the exception of patient matching, all of the statistical analyses were performed using the SPSS, version 16.0, software (IBM, Armonk, NY, USA). Statistical significance was set at $P < 0.05$.

Results

Demographic and clinicopathological characteristics

A total of 228 HCC patients with chronic HBV infection were included in our study. Among these patients, the TACE group consisted of 126 patients, and the TACE-IFN-α consisted of 102 patients. The demographic and baseline clinicopathological data are shown in Table 1. The TACE times are 2.2±1.2 and 2.1±1.1 in TACE group and TACE--IFN-α group, respectively. The two groups did not differ significantly with regard to sex, age, liver function, tumor characteristics, serum albumin level, total bilirubin level, prothrombin time, platelet count, HBV DNA level, serum AFP level and TACE times. All of the patients were scored as stage B/C according to the Barcelona Clinic Liver Cancer (BCLC) staging system. The postoperative AFP level of each patient was < 20 ng/mL. The median follow-up period was 14 months, and the range was 9.6 to 72.3 months.

Recurrence and survival

Sixty-three (61.8%) of the patients in the TACE-IFN-α group and 107 (84.9%) of the patients in the TACE group suffered an HCC recurrence ($P < 0.001$). The median time to recurrence was 20 and 18 months for the TACE-IFN-α

and TACE groups, respectively. In both groups, most of the recurrences were intrahepatic ($P < 0.001$). The frequency of intrahepatic and extrahepatic recurrences were not significantly different between the 2 groups ($P = 0.457$; Table 2).

Overall, 164 (71.9%) of the patients included in our study died due to the progression of HCC, which included 62 (60.8%) of the patients in the TACE-IFN-α group and 102 (80.9%) of patients in the TACE groups, respectively. The median OS was 36.3 months (95% CI: 26.5-30.9) for the TACE-IFN-α group and 24.5 months (95% CI: 19.5-28.9) for the TACE group. The intergroup difference in OS was significant ($P = 0.002$ by the log-rank test; Figure 1A). The 3-and 5-year OS rates were 41.2% (95% CI: 40.5-68.2%) and 39.2% (95% CI: 32.5-52.2%), respectively, for the TACE-IFN-α group and 21.4% (95% CI: 30.5-59.8%) and 19.1% (95% CI: 24.5-45.2%), respectively, for the TACE group. The intergroup differences in the 3-and 5-year OS rates were significant ($P = 0.003$ and $P = 0.001$, respectively by the χ^2-test). The 1-year OS rate for the TACE-IFN-α group (74.5%; 95% CI: 65.6-81.6%) was not significantly different than that of the TACE group (71.4%; 95% CI: 63.5-80.6%; $P = 0.07$ by the χ^2-test).

The median DFS period was 17.4 months (95% CI: 19.5-24.9) for the TACE-IFN-α group and 16.7 months (95% CI: 17.5-22.9) for the TACE group. The intergroup

Table 2. Analyses of Recurrence in the TACE-IFN-α and TACE Groups

Variables	TACE-IFN-α (n = 102)	TACE (n = 126)	P
Tumor recurrence	63 (61.8%)	107 (84.9%)	< 0.001
Site of first tumor recurrence			0.961
Intrahepatic	49 (77.8%)	79 (78.5%)	
Extrahepatic	14 (22.2%)	23 (21.5%)	
Present status			
Survivors	40 (39.2%)	24 (19.0%)	0.001
Disease-free survivors	20 (19.6%)	10 (17.5%)	0.01

TACE, transarterial chemoembolization; IFN-α, interferon alpha

Table 3. Prognostic Actors Associated with DFS and OS in the Univariate Analysis

Variables	Recurrence (%)	P of DFS*	Deaths (%)	P of OS*
Men (n = 204)	152 (74.5)	0.546	148 (72.5)	0.588
Women (n = 24)	18 (75.0)		16 (66.7)	
≤ 60 years of age (n = 215)	160 (74.4)	0.146	154 (71.6)	0.156
> 60 years of age (n = 13)	10 (76.9)		10 (76.9)	
Child-Pugh grade				
A (n = 166)	125 (75.3)	0.402	119 (71.7)	0.541
B (n = 62)	45 (72.6)		45 (72.6)	
Active chronic hepatitis (n = 154)	132 (85.7)	0.008	126 (81.8)	0.048
Inactive chronic hepatitis (n = 74)	38 (51.4)		38 (51.4)	
Serum AFP > 400 ng/mL (n = 98)	72 (73.5)	0.032	72 (73.5)	0.217
Serum AFP ≤400 ng/mL (n = 130)	98 (75.4)		92 (70.8)	
Complete tumor capsule (n = 126)	86 (68.3)	0.082	83 (65.9)	0.082
Incomplete tumor capsule (n = 102)	84 (82.4)		81 (79.4)	
1 tumor nodule (n = 125)	80 (64.0)	0.004	75 (60.0)	0.009
> 1 tumor nodule (n = 103)	90 (87.4)		89 (86.4)	
Microvascular invasion (n = 125)	108 (86.4)	0.001	112 (89.6)	0.036
No microvascular invasion (n = 103)	62 (60.2)		52 (50.5)	
No liver cirrhosis (n = 33)	14 (42.4)	0.019	15 (45.5)	0.005
Liver cirrhosis (n = 195)	156 (80.0)		149 (76.4)	
BCLC stage B (n = 103)	60 (58.3)	0.007	55 (53.4)	0.006
BCLC stage C (n = 125)	110 (88.0)		109 (87.2)	
TACE-IFN-α group (n = 102)	63 (61.8)	0.026	62 (60.8)	0.028
TACE group (n = 126)	107 (84.9)		102 (80.9)	

DFS, disease-free survival; OS, overall survival, AFP, α-fetoprotein; HBV, hepatitis B virus; BCLC, Barcelona clinical liver Cancer; TACE, transarterial chemoembolization; IFN-α, interferon alpha; *Determined using the log rank test

difference in DFS was not significant ($P = 0.054$ by the log-rank test; Figure 1B). The 1-, 3-, and 5-year DFS rates for the TACE-IFN-α group were 38.2% (95% CI: 29.5-47.2), 23.5% (95% CI: 22.4-37.3%), and 19.6% (95% CI: 20.1-32.8%), respectively. The 1-, 3-, and 5-year DFS rates for the TACE group were 36.5% (95% CI: 28.1-46.8%), 20.6% (95% CI: 20.8-35.4%), and 17.5% (95% CI: 18.9-30.8%), respectively. The intergroup differences in the 1-, 3-, and 5-year DFS rates were not significant ($P = 0.064$ by the χ^2 test).

Prognostic factors associated with survival

The univariate analyses showed that OS was associated with chronic hepatitis, the number of tumor nodules, microvascular invasion, liver cirrhosis, the BCLC stage, and the TACE and IFN-α combination therapy (Table 3). The multivariate analyses showed that chronic hepatitis ($P = 0.046$), the number of tumor nodules ($P = 0.007$), microvascular invasion ($P = 0.003$), liver cirrhosis ($P = 0.039$), the BCLC stage ($P = 0.004$), and the TACE and IFN-α combination therapy ($P = 0.032$) were independent predictors of OS (Table 4).

The univariate analyses showed that DFS was associated with chronic hepatitis, serum level of AFP, the number of tumor nodules, microvascular invasion, liver cirrhosis, the BCLC stage, and the TACE and IFN-α combination therapy (Table 3). The multivariate analyses showed that chronic hepatitis ($p = 0.046$), the serum level of AFP, the number of tumor nodules ($p = 0.007$), microvascular invasion ($p = 0.003$), liver cirrhosis ($p = 0.039$), the BCLC stage ($p = 0.004$), and the TACE and IFN-α combination therapy ($p = 0.032$) were independent predictors of OS (Table 4).

Adverse effects

Complications during TACE treatment included fever (≥ 38°C), pain, vomiting, reduced leukocyte count, increased serum level of alanine aminotransferase (ALT), increased serum level of bilirubin, ascites, gastrointestinal hemorrhage, encephalopathy, pleural effusion, liver abscess, and spontaneous bacterial peritonitis. The complication rate was 10.32% (13/126) in the TACE-IFN-α group and 10.78% (11/102) in the TACE group, and the intergroup difference was not significant ($P > 0.05$). No treatment-related deaths occurred in either group.

The most common adverse effects of IFN-α treatment were fever, fatigue, myalgia, leucocytopenia, and thrombocytopenia, which happened in almost every patient on the first administration. Less common adverse effects were elevated ALT, alopecia, depression, and hyperthyroidism; these were rarely noted. Thirteen patients had repeated fever after each injection of IFN-α throughout the treatment period, and five patients stopped the IFN-α treatment because their hematologic parameters did not improve; Twenty-seven patients had to temporarily reduce their dose of IFN-α because of leucocytopenia and thrombocytopenia. IFN-α treatment was continued at full dose in the rest of the patients. Elevated ALT levels were found in 12 patients; the highest level reached being 180 U. The dose of IFN-α was decreased in six patients whose ALT was >120 U, but this returned to former treatment, when ALT levels decreased to 120 U. No patient stopped the IFN a treatment because of elevated ALT levels. Alopecia was not reported in all patients, and depression was reported in two. No specific treatment was given to these patients because alopecia or depression was not severe. No death was related to the side effect of IFN-α.

Table 4. Prognostic Factors Associated with DFS and OS in the Multivariate Analysis

Independent factors	OS			DFS		
	Adjusted HR	95% CI	P	Adjusted HR	95% CI	P
Active chronic hepatitis	1.020	0.804-1.624	0.046	1.200	1.080-1.724	0.001
Number of tumor nodules	1.367	1.068-4.227	0.007	1.947	1.907-8.602	0.005
Microvascular invasion	1.360	1.204-1.894	0.003	3.024	2.826-10.821	0.009
Liver cirrhosis	1.107	1.014-4.619	0.039	1.290	1.137-4.621	0.0213
BCLC stage	1.064	1.005-2.048	0.004	1.665	1.305-2.048	0.003
TACE + IFN-α	1.535	1.402-2.716	0.032	1.106	1.002-3.761	0.039

BCLC, Barcelona clinical liver Cancer; TACE, transarterial chemoembolization; IFN-α, interferon alpha

Discussion

HCC is the fifth most common type of cancer and the third leading cause of cancer-related deaths worldwide. Although surgical resection is the first-line treatment for HCC, postoperative survival is low due to tumor recurrence (Shen et al., 2013). In our current study, we found that TACE-IFN-α combination adjuvant chemotherapy prolonged the time to recurrence and improved OS after curative resection in patients with HBV-related HCC, compared with TACE therapy alone. This finding was substantiated by the results of the matching analysis based on stratified propensity scores and the conventional univariate and multivariable regression analyses. These statistical methods for controlling confounders can yield extremely different estimates of treatment effects (Kim et al., 2009).

TACE is one of the preferred methods of treating patients with advanced stage HCC in China. TACE not only directly kills tumor cells, but also blocks the blood supply to the tumor. The effect of preoperative TACE on the short-and long-term outcome of resectable HCC is controversial. Preoperative TACE has comparable intraoperative and short-term outcomes but more overall cost due to repeated TACE, and the procedure did not significantly improve the overall or tumor-free survival rate. Preoperative TACE should not, therefore, be recommended as a routine procedure before resection for resectable HCCs particularly in cases due to underlying HBV (Jianyong et al., 2014). The survival benefit of postoperative adjuvant TACE remains controversial. To investigate the survival effect of postoperative adjuvant TACE on the prognosis of HBV-related HCC patients (stage B, the Barcelona Clinic Liver Cancer staging), and a study demonstrated postoperative adjuvant TACE improves the survival of patients with HBV-related HCC (stage B) after curative resection compared to surgery only (Li et al., 2014). TACE has definite therapeutic effects for the treatment of HCC after curative resection, especially in patients with moderate to advanced inoperable HCC who are at high risk of recurrence. In patients who had high risks of residual tumor or intrahepatic metastasis in remnant liver, adjuvant TACE could improve their survival due to therapeutic actions on the residual tumor. However, in patients with lower risks of residual tumor or intrahepatic metastasis, adjuvant TACE might have less usefulness or even worse actions due to deterioration of remnant liver function (Lencioni, 2012; Breuning et al., 2013). The aim of TACE treatment is two-fold. The first

aim is to deliver high-dose chemotherapy to the vascular bed of the tumor, and the second aim is to prolong the effects of the chemotherapeutic drugs within the tumor (Martin et al., 2012). The first aim is accomplished by placing a catheter in the branch of the hepatic artery nearest the tumor without excluding the tumor margins (selective catheterization). Before the chemotherapy mixture is infused, it is usually mixed with lipiodol, which increases the viscosity and x-ray visibility of the mixture. The increased viscosity of the chemotherapy mixture and the infusion of embolization particles immediately following chemotherapy infusion slows the blood flow through the tumor tissues, and prolongs the chemotherapy-tumor interaction, thereby accomplishing the second aim.

Studies have shown that TACE increases the concentration of chemotherapy drugs in the tumor 10 to 100 times that of systemically administered drugs, resulting in a greater antitumor response. In addition, the systemic blood level of the chemotherapy drugs are reduced, compared with orally or parenterally administered drugs, reducing toxicity-related side effects (Ippolito et al., 2010). However, a clinical study found that adjuvant TACE provided no significant benefit in HCC patients who lacked significant risk factors for recurrence (Zhong et al., 2010). Our results showed that TACE was beneficial in patients with risk factors for recurrence, which included large tumor size (≥ 5 cm), narrow resection margin (≤ 1.0 cm), the presence of satellite tumor nodules, cirrhosis, and microvascular invasion. Xi et al also reported that TACE adjuvant chemotherapy significantly improved survival in patients with risk factors for recurrence, including large tumor size, presence of satellite tumor nodules, and narrow resection margins (Xi et al., 2012).

A high HBV load and increased ALT levels are the most important correctable risk factors for HCC (Tang et al., 2013). A recent study showed that IFN-α treatment improved survival in patients at high risk of HCC recurrence (Poortahmasebi et al., 2014). IFN-α therapy after curative resection has also been shown to prevent recurrence and improve OS in patients with HBV-related HCC (Qu et al., 2010). A recent study conducted in Japan indicated that adjuvant hepatic arterial infusion chemotherapy using 5-FU and IFN-α reduced recurrence after curative resection, and the findings of that study may have been influenced by a small sample size (n = 33 in the combined therapy group) (Kumamoto et al., 2013). In 27 HCC patients with large tumors and multiple intrahepatic metastases, and TACE and IFN-α combination therapy after tumor resection and debulking surgery improved

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long-term survival in HCC patients (Tanaka et al., 2013). The findings of our current study support the use of TACE and IFN-α combination therapy for treating patients with HBV-related HCC after curative resection. No treatment-related deaths occurred in either the TACE-IFN-α or TACE groups in our study. Therefore, TACE and IFN-α combination therapy is safe for the postresection treatment of HBV-related HCC in patients who are at high risk of recurrence.

In our subgroup analysis of the TACE-IFN-α group, the median OS period was significantly different between the TACE and TACE-IFN-α groups. A systematic review of randomized trials indicated that adjuvant IFN-α therapy following curative treatment of HBV-and HCV-related HCC provided significant benefit (Sun et al., 2013). Another randomized clinical trial also suggested that IFN-α treatment improved the OS of patients with HBV-related HCC after curative resection, suggesting that recurrence was reduced (Sun et al., 2006). A study of chronic hepatitis due to an active HBV infection showed that serum levels of ALT > 40 IU/L and HBV DNA >10^3 copies/mL significantly correlated with HCC (Lin et al., 2010). Therefore, we recommend adjuvant IFN-α therapy for HCC patients with a serum level of HBV DNA level ≥ 10^4 copies/mL after resection, and the administration of TACE-IFN-α combination adjuvant therapy and antiviral therapy for preventing HCC recurrence in high-risk patients.

Our results showed that the survival rate in the TACE-IFN-α group was significantly higher than that of the TACE group, and a significant difference in the recurrence patterns occurred between the 2 groups. The rate of intrahepatic recurrence was significantly lower in the TACE-IFN-α group than that in the TACE group. In addition, the site of the first tumor recurrence in the TACE group did not significantly differ from that of the TACE group (Sakon et al., 2002).

In a previous study, TACE and IFN-α combination chemotherapy demonstrated a high response rate for the treatment of advanced HCC, with a disease control rate of 63% reported for 5-FU-based TACE and IFN-α used in combination (Nagano et al., 2007). The results of our current study showed that TACE and IFN-α combination chemotherapy had a more positive effect on the outcomes of HCC patients at high risk for recurrence after curative resection, compared with that of patients who lacked high-risk factors. The median OS in the TACE-IFN-α group was significantly longer (36.3 months) than that of the TACE group (24.5 months). The 3-and 5-year OS rates for the TACE-IFN-α group were higher than those for the TACE group. The results of our retrospective cohort study provide new insights into the treatment of hepatitis B-related HCC in patients who are at high risk of recurrence.

Our univariate and multivariate analyses showed that the TACE and IFN-α combination therapy, active HBV infection, the number of tumor nodules, microvascular invasion, liver cirrhosis, and the BCLC stage were independent predictors of OS and DFS in patients with HBV-related HCC. Previous studies have also shown that active hepatitis, liver cirrhosis, and the BCLC stage

were prognostic factors for recurrence and survival in HCC patients following hepatic resection (Hung et al., 2013; Hu et al., 2014; Zhou et al., 2014). However, our results showed that the median DFS of the patients who received the TACE and IFN-α combination chemotherapy (17.4 months) was not significantly longer than that of the patients who received TACE therapy alone (16.7 months), and the intergroup differences in the 1-, 3-, and 5-year DFS rates were not significant. The use of a cohort of patients that was ethnically homogenous limits the generalization of our current findings. Furthermore, for reasons that remain unclear, some HCC patients exhibited a low response rate to the TACE and IFN-α combination therapy.

The ability to identify patients who are most likely to benefit from adjuvant therapies may confound studies of the use of such therapies for the treatment of HCC. The miR-26 expression status of HCC patients is associated with survival and response to IFN-α adjuvant therapy. Individualized antiviral therapy is required for regulating the expression of miR-26 to prevent patients from being treated with IFN-α whose survival is unlikely to improve (Ji et al., 2009). Patients with low RIG-I expression had shorter survival and poorer response to IFN-α therapy, suggesting that RIG-I is a useful prognosticator of IFN-α response in HCC patients. Therefore, RIG-I expression can be used to identify HCC patients likely to exhibit improved response to IFN-α adjuvant therapy, as well as those likely to respond better to other treatment strategies (Hou et al., 2014).

In conclusion, our observational study aimed to minimize bias and approximate a randomized trial by basing our analysis on propensity score estimates. The results indicated that the TACE and IFN-α combination chemotherapy improved OS in patients with HBV-related HCC who were at high risk of recurrence after curative resection by postponing recurrence. As a first-or second-line treatment for HCC, the TACE and IFN-α combination chemotherapy may improve survival more than treatment with TACE alone, especially in patients with HBV-related HCC who are at high risk of recurrence. Future prospective randomized trials are required to confirm that TACE and IFN-α combination chemotherapy represents an improvement to the current standard of care for patients with HBV-related HCC who are at high risk of recurrence.

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