RESEARCH ARTICLE

Rate and Predictive Factors for Sustained Complete Response after Selective Transarterial Chemoembolization (TACE) in Patients with Hepatocellular Carcinoma

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Abstract

Background: To determine the effectiveness and performance of selective conventional transarterial chemoembolization (TACE) and analyze the potential predictive factors of sustained complete response (CR) for patients with hepatocellular carcinoma (HCC). **Materials and Methods:** Total of 52 patients with HCC (33 males, 19 females; mean age 64.0 ± 9.6 years) who underwent 81 sessions of selective TACE between November 2015 and March 2017 at Songklanagarind hospital were reviewed. The Kaplan-Meier method was used to describe CR rates at various time points. Univariate and multivariate logistic regression models were performed to determine the predictive factors for sustained CR at six months. **Results:** The CR rates after selective TACE at 1, 4, 6, 9 and 12 months were 87%, 81%, 62%, 40% and 31%, respectively. Univariate and multivariate analyses demonstrated that alpha fetoprotein level <100ng/ml, a tumor size in summation ≤ 30 mm, ≤ 2 sessions of selective TACE and unilobar involvement had a significantly higher odds of sustaining complete response at six months (p =0.018, 0.031, 0.032, and 0.044, respectively). **Conclusions:** Selective TACE has a good therapeutic results and can sustained complete response in selected HCC patients. Serum AFP≤ 100 ng/ml, a few sessions of selective TACE, tumor size in summation ≤ 30 mm and unilobar involvement were favorable predictive factors for sustained complete response of HCC patients.

Keywords: Complete response- predictive factors- selective TACE- Hepatocellular carcinoma

Introduction

Hepatocellular carcinoma (HCC) is a common malignancy worldwide. It is more common in men than in women and also is the second leading cause of tumor-related deaths after lung cancer (Torre et al., 2015). The incidence of HCC is increasing worldwide due to rising prevalence of risk factors such as excessive alcohol consumption and dissemination of hepatitis B and C virus infections (Bosch et al., 1999). Patients with HCC often present at a late stage, resulting in little or no chance of cure (Llovet et al., 1999; Bruix and Llovet, 2002; Trinchet and Beaugrand, 1997; Bruix et al., 2001). Moreover, a high proportion of early stage patients relapse after receiving first-line treatment (Lencioni, 2012).

Conventional transarterial chemoembolization (TACE) is the standard treatment for patients with intermediate-stage HCC, relatively preserved liver function, no cancer-related symptoms, absence of vascular invasion, and no extrahepatic metastasis (Llovet et al., 2008). The procedure precisely administers chemotherapeutic drugs and iodized oil (Lipiodol,

Guerbet) to the tumor and blocks the tumor-feeding arteries with gelatin sponge particles. This results in combined cytotoxic and ischemic effects on the tumor cells. Moreover, TACE has been widely performed for the treatment in unresectable HCC patients and also indicated in advanced-stage HCC with partial main portal vein thrombosis (Bruix and Sherman, 2011; Arii et al., 2010). Selective TACE with catheterization at the tumor-feeding subsegmental hepatic artery gives significantly lower local recurrent rate (Miyayama et al., 2007; Iwamoto et al., 2003), reduces total dose of iodized oil and minimizes liver toxicity (Matsui et al., 1993) compared to non-selective TACE.

Complete response by non-selective TACE was poor in former decade (Llovet et al., 2002) but rates later improved with selective TACE (Miyayama et al., 2007; Takayasu et al., 2001; Miyayama et al., 2009; Matsui et al., 2010). For middle income countries with larger tumor size and more limited resources, the effectiveness of selective TACE has never been documented. Complete response at the initial assessment was found to be a good predictor of overall survival among patients with inoperable HCC (Kim et al.,

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2015). Few previous studies reported factors associated with complete response in patients with HCC treated by non-selective TACE (Jeong et al., 2017; Yamakado et al., 2012) and information from selective TACE was also lacking. The objective of this study was therefore to assess the effectiveness of selective TACE in terms of complete response rate in HCC patients, and to find predictive factors of sustained complete response at six months.

Materials and Methods

Patient selection

Approval to conduct this study was obtained from the institutional ethics committee (60-220-07-1). The study was carried out at Songklanagarind hospital, a tertiary care hospital in southern Thailand, where selective TACE was introduced in November 2015.

Diagnosis of HCC, we followed the American Association for the Study of Liver Diseases criteria (Bruix and Sherman, 2011). Liver lesions larger than 1 cm in diameter were evaluated by dynamic magnetic resonance imaging or multidetector computed tomography (MDCT) scan using contrast media. If the imaging appearance was typical of HCC, no further diagnostic procedure was attempted.

All patients underwent blood investigations including complete blood count, liver function test, coagulation test, viral markers of hepatitis B and C infection, and serum alpha-fetoprotein (AFP). The assessment of chronic liver disease was based on the Child-Pugh classification system (Pugh et al., 1973).

Patient inclusion criteria were as follows: (a) adult HCC patients with hepatic cirrhosis, (b) patients treated with selective TACE with catheterization at the subsegmental hepatic artery feeding the tumor, (c) tumor size $\leq$ 7cm, and (d) number of distinct tumor nodules $\leq$ 5, (e) patient was ineligible for surgical resection or transplantation. Patients with extrahepatic metastasis, infiltrative tumors, and severe arterioportal shunt were excluded. We also excluded any patient who did not have any follow-up assessments performed at six months.

Chemoembolization steps and techniques

All eligible HCC patients were invited to receive selective conventional TACE (TACE), defined as catheterization at the subsegmental hepatic artery performed by two interventional radiologists through the transfemoral route. Superior mesenteric artery and celiac axis arteriogram were selective at the beginning of procedure using a 5Fr selective catheter (Cobra or MIK catheter) and a 0.035-inch J-tip Terumo guidewire. We performed selective catheterization to the tumor feeding hepatic arteries or in extrahepatic collaterals as distal as possible in each tumor lesion using a microcatheter (A 1.98-Fr tip Asahi Masters Parkway Soft microcatheter from Asahi, a 2.0-Fr tip Progreat microcatheter from Terumo or a 2.4-Fr tip Renegrade STC microcatheter from Boston Scientific) with coaxial technique. We slowly administered the mixture of iodized oil; range 4-16 ml (Lipiodol, Guerbet), the doxorubicin hydrochloride; range 10-40 mg (Adriamycin, Pfizer) under real time monitoring on Digital Subtraction Angiography (Phillips AlluraClarity FD20). The amount of anticancer-in-oil-emulsion was determined by total tumor size and number of nodules. Subsequently, this feeding artery was embolized using gelatin sponge particles. We completed the procedure when the tumor feeding branch was completely obstructed and tumor staining from digital subtraction angiography completely disappeared.

Outcome and imaging follow up

All patients were followed-up after selective TACE with detailed clinical examination, blood chemistry, and imaging examination (dynamic magnetic resonance imaging or 4-phase contrast-enhanced computed tomography scan) one month after the initial procedure. If no definite evidence of residual tumor was shown, then imaging examination was performed at 3-month intervals thereafter. The decision to repeat the TACE procedure was based on tumor response, stage of the disease, and patient's tolerance.

Tumor response was defined according to modified Response Evaluation Criteria in Solid Tumors (mRECIST) guideline (Lencioni and Llovet, 2010). Complete response(CR) defined as disappearance of any intratumoral arterial enhancement in target lesions (Lencioni and Llovet, 2010). Tumor size in summation was defined as the sum of diameters of two target lesions in the liver.

Assessment of response was evaluated independently by two radiologists with thirteen and five years of experience, respectively and the final decisions were achieved by consensus. All measurements were performed using the electronic tools available at the workstation (i.e., calipers for size measurements and circular regions of interest for attenuation measurement).

TACE-related morbidity/mortality was defined as any complication (including death) within two weeks of each session of TACE.

Statistical analysis

Data analyses were performed using R software (version 3.3.3). Numerical data are presented descriptively using the central tendency (mean, median and mode) and a measure of dispersion (standard deviation and range).

The probability of achieving complete response was estimated using the Kaplan-Meier method. The overall complete response rates at 1, 4, 6, 9 and 12 months was determined.

The comparison of demographic data and clinical factors were initially assessed with univariate analysis. Subsequently, all variables having a p-value $\leq$ 0.2 from the univariate analysis were entered into the initial multivariate logistic regression model.

Results

Between November 2015 and March 2017, 69 HCC patients undergoing selective TACE were identified. After exclusion criteria were applied, 52 patients with total 71 HCC nodules (mean diameter, 2.6 cm $\pm$ 1.4; range, 1.0-6.9 cm; median diameter, 2.0 cm) remained and were included in the analysis. Figure 1 shows a flow diagram of the study.
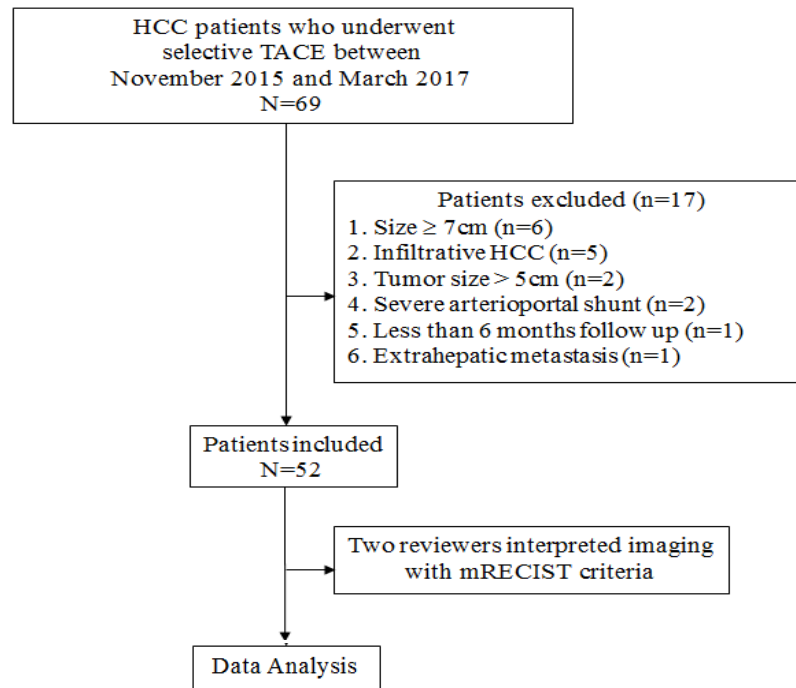
Figure 1. Flow Diagram of the Study. HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; mRECIST, modified Response Evaluation Criteria in Solid Tumors

A total of 17 patients were excluded due to tumor size ≥ 7 cm (6 patients), infiltrative HCC (5 patients), number of tumors > 5 (2 patients), severe arterioportal shunt (2 patients), loss to follow up (1 patient) and presence of extrahepatic metastasis (1 patient).

A total of 81 sessions of selective TACE were performed (one session in 32 patients, two sessions in 15 patients, three sessions in 2 patients, four sessions in 2 patients, and five sessions in 1 patient). Demographic characteristics of the patients are shown in Table 1. There were 33 males and 19 females and the mean age was 64.0 ± 9.6 years (range 41-90 years). Hepatitis B viral infection (HBV) was found in 29 (55.8%) patients. The numbers of patients with Child Pugh classes A and B were 42 (80.8%) and 10 (19.2%), respectively. Thirty-seven patients (71.2%) had an AFP level ≤ 100 ng/ml. A solitary nodule was present in 38 (73.1%) patients and multiple nodules in 14 (26.9%) patients. The mean tumor size in summation was 32.6±18.5 mm (range: 10-95 mm).

Patients were followed up for a mean period of 11.2±4.7 months (range: 6–23 months; median: 9.8 months). All treatment-related adverse toxicities were classified as minor. Post embolization syndrome (fever, pain, and increased white blood cell count) developed in 7 patients without requiring extended stay or re-admission. Biloma occurred in 1 patient and was followed up without any treatment due to no symptom. One died from ischemic bowel disease at 9 months. Remaining 51 patients were alive at the time of analysis.

Total 151 computed tomography (CT) and 31 magnetic resonance (MR) images in 52 patients with hepatocellular carcinoma were reviewed to determine tumor response based on mRECIST. Figure 2 shows the Kaplan-Meier curve depicting the probability of maintaining complete response since the first selective TACE session. The cumulative complete response of the

target lesions maintaining probabilities at 1, 4, 6, 9 and 12 months were 87%, 81%, 62%, 40% and 31%, respectively.

Table 2 summarizes demographic characteristics and imaging data of patients by survival status at the end of the 6th month. Patient with alpha fetoprotein level <100ng/ml, less than two sessions before achieving complete response, a solitary nodule and with a tumor size in summation ≤ 30 mm had a significantly higher odds of sustaining complete response at six months.

Discussion

Most of the patients in this series were males, had hepatitis B related cirrhosis and BCLC stage A with
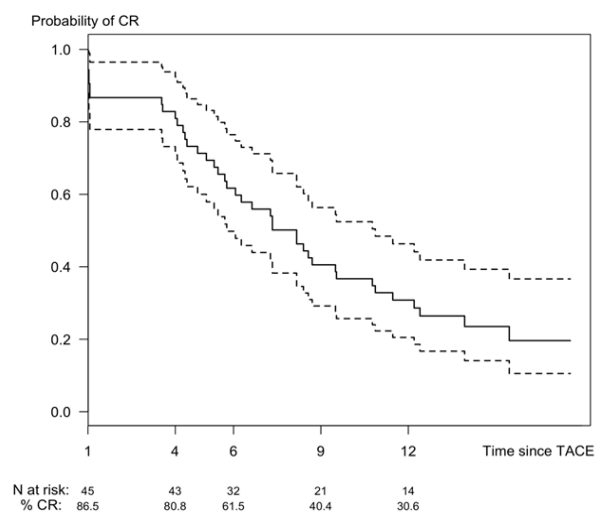

Figure 2. Kaplan-Meier Survival Curve Depicting the Probability of Sustained Complete Response for Patients with Hepatocellular Carcinoma Undergoing Selective TACE (n=52).

Table 1. Demographic Characteristics and Clinical Profiles of Hepatocellular Carcinoma Patients before Undergoing Selective TACE (n=52)

Variable	Frequency	Percentage
Age (years)		
Mean (SD)	64.0 (±9.6)	
Range	41-90	
Sex		
Male	33	63.5
Female	19	36.5
Etiology		
HBV	29	55.8
HCV	7	13.5
Alcohol	4	7.7
Hepatitis + Alcohol	2	3.8
Other	10	19.2
Child Pugh class	42	80.8
A	10	19.2
B		
Alpha Fetoprotein (ng/ml)		
≤ 100	37	71.2
>100	15	28.8
Albumin (g/dL)		
> 3.5	38	73.1
≤ 3.5	14	26.9
Total bilirubin (mg/dL)		
≤ 2	49	94.2
> 2	3	5.8
Prothrombin time (sec)		
> 13.5	27	51.9
≤ 13.5	25	48.1
Tumor burden		
Solitary	38	73.1
Multiple	14	26.9
Tumor size in summation (mm)		
≤ 30	27	51.9
30-50	18	34.6
> 50	7	13.5
BCLC stage		
A	5	48.1
B	19	36.5
C	8	15.4

BCLC, Barcelona Clinic Liver Cancer

normal range of albumin level, and low levels of AFP and total bilirubin before undergoing selective TACE. After performing the procedure, the cumulative complete response rate at 6 months was 62%. The strongest predictor was number of TACE session ≤ 2 times, and the weakest was tumor size in summation ≤ 30 mm. Number of tumor nodules was significant in univariate analysis but not in multivariate logistic regression model.

TACE is the most common mode of treatment in Thailand because of a large number of patient presenting

Table 2. Comparison of Demographic and Clinical Factors and Results of Univariate Analysis among Patients who Sustained Complete Response at 6 Months since Undergoing Selective TACE Compared to Those who Did not

Variables	Sustained CR (n=32)	Did not sustain CR (n=20)	Odds Ratio (95% CI)	P value
Gender				
Male	20 (62.5)	13 (65)	1	0.855
Female	12 (37.5)	7 (35)	1.1 (0.35-3.57)	
Age (years)				
≤ 65	16 (50)	12 (60)	0.67(0.22-2.07)	0.481
> 65	16 (50)	8 (40)	1	
Etiology				0.522
Alcohol	2 (6.2)	2 (10)	1	
HBV	20 (62.5)	9 (45)	2.22 (0.27-18.37)	
HCV	5 (15.6)	2 (10)	2.5 (0.19-32.19)	
Hepatitis + Alcohol	1 (3.1)	1 (5)	1 (0.03-29.81)	
Others	4 (12.5)	6 (30)	0.67 (0.06-6.87)	
Child-Pugh Class				
A	26 (81.2)	16 (80)	1.08 (0.26-4.44)	0.912
B	6 (18.8)	4 (20)	1	
Alpha fetoprotein (ng/ml)				
≤100	27 (84.4)	10 (50)	5.4 (1.48-19.73)	0.008*
>100	5 (15.6)	10 (50)	1	
Albumin				
≤3.5	9 (28.1)	5 (25)	1	0.804
>3.5	23 (71.9)	15 (75)	0.85 (0.24-3.04)	
Total bilirubin				
>2	1 (3.1)	2 (10)	1	0.309
≤2	31 (96.9)	18 (90)	3.44 (0.29-40.71)	
Prothrombin time				
>13.5	16 (50)	11 (55)	1	0.725
≤13.5	16 (50)	9 (45)	1.22 (0.4-3.75)	
Number of sessions				
≤2	31 (96.9)	16 (80)	7.75 (0.8-75.23)	0.045*
>2	1 (3.1)	4 (20)	1	
Number of tumor nodules				
>1	4 (12.5)	10 (50)	1	0.003*
1	28 (87.5)	10 (50)	7.00 (1.79-27.44)	
Tumor size in summation(mm)				
≤30	21 (65.6)	6 (30)	4.45 (1.34-14.83)	0.011*
>30	11 (34.4)	14 (70)	1	
Lobar involvement				
Unilobar	31 (96.9)	17 (85)	5.47 (0.53-56.75)	0.122
Bilobar	1 (3.1)	3 (15)	1	
Subcapsular location				
Yes	26 (81.2)	16 (80)	1	0.912
No	6 (18.8)	4 (20)	0.92 (0.23-3.78)	
Portal vein thrombosis				
Yes	5 (15.6)	3 (15)	1	0.951
No	27 (84.4)	17 (85)	0.95 (0.2-4.51)	
Near portal vein				
Yes	5 (15.6)	5 (25)	1	0.409
No	27 (84.4)	15 (75)	1.8 (0.45-7.23)	

*, Likelihood ratio test; CR, complete response. HBV, hepatitis B virus; HCV, hepatitis C virus

Table 3. Multivariate Logistic Regression Model Predicting Sustained Complete Response at 6 Months and Prognostic Factors in HCC Patients Undergoing Selective TACE

Predictor	OR (95% CI)	P-value*
Alpha Fetoprotein ≤ 100ng/ml	5.4 (1.48-19.73)	0.018
Tumor size in summation ≤ 30 mm	4.45 (1.34-14.83)	0.031
Number of TACE sessions ≤ 2	7.75 (0.80-75.23)	0.032
Unilobar involvement	5.47 (0.53-56.75)	0.044

*, Likelihood ratio test; OR, Odds ratio; CI, Confidence interval

with large and multifocal HCCs. It was accounted 13-41% of total treatment of HCC in Thailand (Chonprasertsuk et al., 2017). Therefore, our study used the tumor size ≤ 7cm, and number of distinct hypervascular tumors ≤ 5 to be the inclusion criteria. In contrary with the previous studies from Japan (Miyayama et al., 2007; Matsui et al., 2010) included patients with HCC who had fewer than three hypervascular tumors smaller than 5cm in diameter. Moreover, there are some differences in the background of patients. Chronic HBV infection is the most common cause of HCC in our study, whereas HCV infection is the major risk factor in Japan study (Miyayama et al., 2007).

Selective TACE, although incurring increased costs and procedural time for catheterization, leads to better clinical outcomes when compared with non-selective TACE (Yamakado et al., 2012). Lipiodol or iodized oil in TACE can deeply pass into surrounding portal venules and hepatic sinusoids through peribiliary plexus resulting in low rates of local tumor recurrence (Miyayama et al., 2007). In our study, the changes in complete response rates over time were similar to those in other previous studies from Japan (Miyayama et al., 2007; Matsui et al., 1993; Takayasu et al., 2001; Miyayama et al., 2009; Matsui et al., 2010) and were better than the European randomized controlled trials on non-selective TACE by Llovet et al., (2002), which yielded partial response rates of 15-55%. Selective TACE can limit the damage to liver parachyma at the subsegment level, thus reducing the complications. Post embolization syndrome, for example, could be reduced from 60-80% in two previous reports (Raoul et al., 2014; Ebied et al., 2014) to 13.5% in our study. Hepatic failure from liver ischemia was also reduced from 49% in a previous study (Ebied et al., 2014) to 0% in our study.

Assessment at 1-month follow up may be too early to determine whether patients achieve complete response due to non-specific Lipiodol accumulation surrounding the tumor, and washout of Lipiodol cannot be evaluated by computed tomography scan 4 weeks after the procedure (Kim et al., 2015). Therefore we used a sustained CR at 6-months follow up for recognition of predictive factors.

Serum AFP at the time of TACE is a predictor for maintaining complete response at six months. AFP plays important roles in both immune system inhibition and encouraging cancer cell growth. High serum AFP showed a poorer differentiation grade of HCC and needs to be closely followed up with consideration of additional treatments (Okuda et al., 2001; Veltri et al, 2006; Evdokimova et al., 2007). On the other hand, low serum AFP may indicate a less aggressive tumor and thus lower rate of tumor recurrence.

Difficulty in performing TACE varies case by case, depending on various factors such as tumor size, number of nodules, location, and spreading pattern of the tumor. Difficult cases are more likely to require more sessions of TACE to achieve complete response. The non-cancerous liver tissues are also more damaged by multiple sessions of TACE. Two consecutive poor responses to TACE was a criterion for TACE failure/refractoriness (Kudo et al., 2014; Raoul et al., 2014). These and other previous findings related to multiple TACE sessions (Kim et al., 2015) could explain why the number of TACE sessions is a predictive factor for sustained CR in our results.

Larger tumors usually have more satellite lesions or daughter nodules making it difficult for selective TACE to achieve completely response. Smaller sized tumors, especially those less than 30 mm, had a high complete response rate, as a result previously reported by Ebied et al., (2003). In our study, tumor size in summation ≤ 30 mm was a predictive factor for sustained complete response at six months, a result similar to the study by Golfieri et al., (2013) who reported that tumors ≤50 mm achieved the best response to selective TACE. For the same reason, unilobar tumors can be treated effectively with selective TACE by occluding tumor supplying arteries those that are not relatively complex compared with multiple and bilobar tumors.

This study was limited by its retrospective nature. The number of patients in this series was also relatively small and the follow up time was relatively short. The technical factors in TACE such as grading of portal vein visualization or safety margin of lipiodol accumulation were not assessed in this study. The study population of this study is quite narrow window of TACE indication, so these selected patient group has relative high tumor response rate.

In conclusion, selective TACE has a lower complication rate, has a good therapeutic results and can sustained complete response in selected HCC patients. Serum AFP≤ 100 ng/ml, a few sessions of selective TACE, tumor size in summation ≤ 30 mm and unilobar involvement were favorable predictive factors for sustained complete response of HCC patients.

Acknowledgements

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