Original Article

Outcome of Transarterial Chemoembolization with 5-Fluorouracil plus Mitomycin C in Hepatocellular Carcinoma Patients : Results of 144 Patients at The King Chulalongkorn Memorial Hospital, Thailand.

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ABSTRACT

Background: Transarterial chemoembolization (TACE) is one of the most common used treatment modality for hepatocellular carcinoma (HCC) patients, especially in patients who can not undergo any curative treatments. Several studies have demonstrated the beneficial impact on survival. To date, the Barcelona Clinic Liver Cancer (BCLC) staging system is the most accepted staging system for HCC which provided treatment strategies according to the stage. Among the stage A, not all the patients were treated with surgery, local ablation or liver transplantation as the guideline for several reasons either unfavorable location of tumor, advanced stage of underlying liver disease, facility of the institution and shortage of organ donors. These patients were usually treated with TACE. In the stage B, which was recommended for TACE, there is still some different in regarding to size and number of tumor between the patients. Not all the stage A and B patients had survival benefit from TACE. Factoirs influencing the survival outcome should be evaluated.

Objectives: To evaluated the outcome of TACE using 5-fluorouracil plus mitomycin C in the different stage of HCC patients based on the BCLC staging system and to evaluate the subgroups of patients in stage A and B who received the most survival benefit from TACE.

Patients and Methods: From January 1998 to November 2003, A total of 144 HCC patients treated only with TACE using 5-fluorouracil plus mitomycin C were analysed retrospectively for survival time in relation to the BCLC staging system.

Results: The one and two years survival rate of the patients in stage A (N = 33) were 66% and 39%, stage B(N = 80) were 45%and 20% and stage C (N = 31) were 13% and 3%,respectively (p = 0.01). Based on the Child Pugh classification, the 1and 2 years survival rate of the stage A patients who wre in Child A (N = 24) were 78% and 45%, In Child B (N = 9) were 33% and 22%, respectively (p = 0.374). For the stage B patients, the 1 and 2 years survival rate in those with single tumor smaller than 10 cm (N = 25) were 50% and 40%, those with single tumor larger than 10 cm or multiple tumors (N = 55) were 40% and 10%, respectively (p = 0.01).

Conclusion : In the BCLC stage A patients, TACE seemed to show the 2 years survival benefit in those with Child A. More data on Child B are needed to evaluate the survival advantage. In the BCLC stage B patients, those with single tumor smaller than 10 cm showed the best 2 years survival benefit than the others.

Key words : transarterial chemoembolization, hepatocellular carcinoma, outcome

[Thai J Gastroenterol 2006; 7(3): 120-125]

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary liver neoplasm. The incidence of HCC is increasing worldwide.[1] In the largest study on natural history of HCC patients by Okuda, the median survival in untreated group was only 1.6 months.[2] In Thailand, where is the high incidence of hepatitis B virus, which has been implicated in HCC carcinogenesis, HCC is one of the leading cause of cancer related mortality especially in males. Data from our Institute show a median survival of the untreated patients only 2.3 months and most of the untreated patients died within 2 years after diagnosed.[3] Curative treatments either resection or percutaneous ablations are reserved for patients with limited disease and compensated underlying liver disease. Now, the most widely accepted criteria for OLT in HCC patients is Milan's criteria (single tumor <5 cm or up to 3 tumors, each <3 cm).[4] Unfortunately, most of the HCC patients in Thailand can not undergo any curative treatment modalities for many reasons either unfavorable location of tumor, unfavorable underlying liver function test, advanced stage of tumor or the shortage of organ donors. Thus, TACE is one of the most common used treatment in these patients due to several data on survival benefit.[5-9] There are variable regimens of chemotherapeutic agents used in TACE, vary among centers. The most common used were single anticancer of cisplatin[10-12], doxorubicin[5,13], epirubicin[14] or mitomycin C.[2,15] Only a few studies demonstrated the efficacy of combination anticancer agents.[16,17] At our hospital, we used combination of 5-fluorouracil plus mitomycin C for TACE in the majority of patients due to the believe that combination anticancers agents are superior to any single agent and this combination regimen give the suitable cost in TACE for Thai HCC patients.

In the early stage HCC patients, defined as a single tumor smaller than 5 cm or upto 3 tumors less than 3 cm in diameter, OLT showed a promising outcome with 75% survival rate after 4 years but more than half of these patients were performed TACE to slow tumor progression befor OLT.[4] To date, there is limited data regarding survival outcome in these group of HCC patients who were treated only with TACE.[8] The aims of this study were to evaluate the outcome of TACE using 5-fluorouracil plus mitomycin C in the differrent stages of HCC patients, based on the Barcelona Clinic Licer Cancer (BCLC) staging system and in patients who eligible for OLT based on Milan's criteria. We used the BCLC staging system because now it is the most widely accepted HCC staging system that identifies those with early HCC who may benefit from curative therapies, those at intermediate or advanced disease stage who may benefit from palliative treatments, as well as those at end-stage with a very poor life expectancy.[18,19]

PATIENTS AND METHODS

A total of 280 HCC patients were performed TACE since January 1998 to November 2003 at The King Chulalongkorn Memorial Hospital, Bangkok, Thailand. Of these, 82 patients were excluded because of having combination therapy with other treatment modalities either surgical resection, percutaneous ablations, systemic chemotherapy or OLT, 39 patients received other anticancer regimens, 12 patients had ruptured HCC and 3 patients had Child-Pugh class C. Thus, a total of 144 patients who only treated with TACE using 5-fluorouracil plus mitomycin C were analysed retrospectively for survival outcome in relation to the BCLC staging system. The diagnosis of HCC were based on histology or typical vascular pattern on dynamic imaging with elevated serum alfafetoprotien (AFP) >400 ng/ml. The BCLC stage A patients (early HCC) were those who have performance status grade 0, single tumor <5 cm or up to 3 tumors <3 cm and Child-Pugh class A-B. The BCLC stage B patients (intermediate HCC) were those who have performance status grade 0, large multinodular tumor and Child-Pugh class A-B. The BCLC stage C patients (advanced HCC) were those who have one of the following characteristics : performance status grade 1-2, vascular invasion or extrahepatic spread. The BCLC stage D patients (end-stage HCC) were those who have performance status grade 3-4 or Child-Pugh class C.

TACE technique

All patients were performed TACE by one of the 3 experted intervention radiologists in our hospital. TACE was performed by transfemoral approach with Seldinger's technique under local anesthesia. Hepatic arteriography and superior mesenteric arterial portovenography were performed to define the size and locations of tumor and to exclude occlusion of the main portal vein. After the right or left hepatic artery feed-

ing the tumnor was identified, the mixture of 10ml Lipiodol (Ultrafluide, Laboratoire Guerbet, Aulnay-Sous-Bois, France) and 20 mg of mitomycin C (Kyowa, Tokyo, Japan) plus 500mg of 5-fluorouracil (Choongwae, Seoul, Korea) were injected slowly under fluoroscopic monitoring followed by absorpable gelatin sponge particles (Spongostan, Johnson & Johnson, Skipton, UK). Successful embolization on the feeding artery was confirmed by angiogram.

Liver biochemistry, complete blood count, renal function, prothrombin time, AFP, chest x-ray and CT scan were obtained at baseline and 4 weeks after every TACE sessions. Patients underwent the next TACE session at 6-8 weeks if there is no objective response by CT scan. TACE was discontinued if any of the following conditions occurred:

1) complete lipiodol staining as evidenced by CT scan (objective response)
2) evidence of new tumor nodule in liver
3) pulmonary metastasis
4) total bilirubin > 3 mg/dl
5) development of main portal vein thrombosis
6) refusal of the further TACE session

Statistical analysis

The primary outcome was the 2-years survival rate. Continuous variables were expressed as mean and compared using Oneway ANOVA test. Categorical variables were compared with Chi-Square test. The survival rate and univariate analysis for 10 baseline variables to identify the predictors of survival were analysed by Kaplan-Meier method and compared by the log-rank test. Finally, all the significant prognostic factors identified from univariate analysis were put into a Cox proportional hazards model for multivariate analysis. Statistical analysis was performed with the SPSS version 13.0 software (SPSS, Chicago, IL).

RESULTS

There were 33 patients in the BCLC stage A, 80 patients in stage B and 31 patients in stage C. The demographic data of these three groups of patients are summarized in Table 1. The patients in stage A were older than stage B and C ($p < 0.05$). There were no statistical differrence in gender and numbers of TACE sessions. The overall 1 and 2 years survival were 43% and 21%, respectively. The acturial one and two years survival rate in stage A were 66% and 39%, stage B were 45% and 20% and stage C were 13% and 3%, respectively ($p < 0.05$) (Table 2 and Figure 1). Most patients died from complication of HCC or end-stage liver disease either rupture HCC, upper gastrointestinal bleeding, sepsis, metabolic acidosis or hepatic encephalopathy. Univariate analysis with log-rank test identified 3 significant prognostic factors : tumor number, albumin and Child-Pugh class (Table 3). With multivariate analysis, only tumor number was statistically significant in the final Cox model. The relative risk of death in patients who had multiple tumor number was 1.48 (95%CI, 1.009-2.192; $p = 0.045$).

The 33 patients in stage A were those who eligible for OLT based on Milan's criteria. Between this group, the 1 and 2 years survival rate in Child Pugh class A (N = 24) were 79% and 46% and in Child Pugh class B (N = 9) were 33.3% and 22.2%, respectively ($p = 0.08$) (Figure 2).

Regarding to the 80 patients in stage B, the one and two years survival rate in those who have single tumor ≤10 cm (N = 25) were 52 % and 40%, in those who have single tumor >10 cm or multiple tumors (N = 55) were 31% and 11%, respectively ($p = 0.04$) (Figure 3).

DISCUSSION

HCC is a relatively silent disease and is frequently associated with cirrhosis. By the time symptoms from the tumor are evident, the tumor is usually extensive and inoperable. In the recent AASLD guideline on the management of hepatocellular carcinoma[19], the BCLC stage A patients are suitable for any curative treatments either resection, percutaneous ablation or OLT. Unfortunately,some patients are not suitable for any curative treatments following this guideline because of unfavorable location of tumor, unfavorable liver function test, experience of each intervention radiologists on

Table 1 Demographic data

	Stage A	Stage B	Stage C
No. of patients	33	80	31
Mean age (yrs.)	63.6	57.4	53.5
Sex (male/female)	25/8	69/11	27/4
Etiology (HBV/HCV)	18/9	46/6	19/2
AFP >400 ng/ml	10	30	22
No. of TACE sessions (mean)	3.1	3.2	2.6

Table 2 Survival rate according to BCLC stages

Stages	Survival			
	6 months	12 months	18 months	24 months
Stage A (N = 33)	94% (31)	66% (22)	51% (17)	39% (13)
Stage B (N = 80)	64% (51)	45% (36)	30% (24)	20% (16)
Stage C (N = 31)	52% (16)	13% (4)	6% (2)	3% (1)

Overall comparisons, Log Rank test; p <0.05
() - numbers of patients

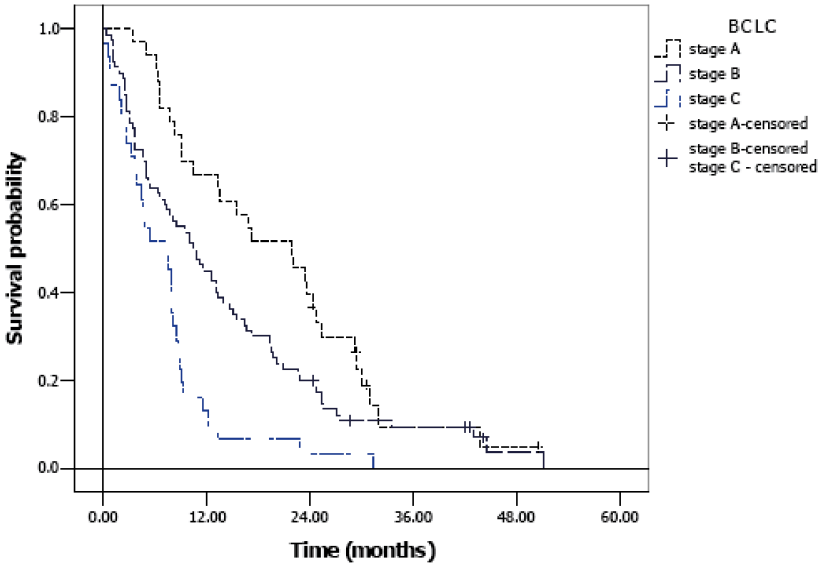


Figure 1 Survival outcome of 144 HCC patients treated with TACE using 5-FU plus mitomycin C according to the BCLC stage.

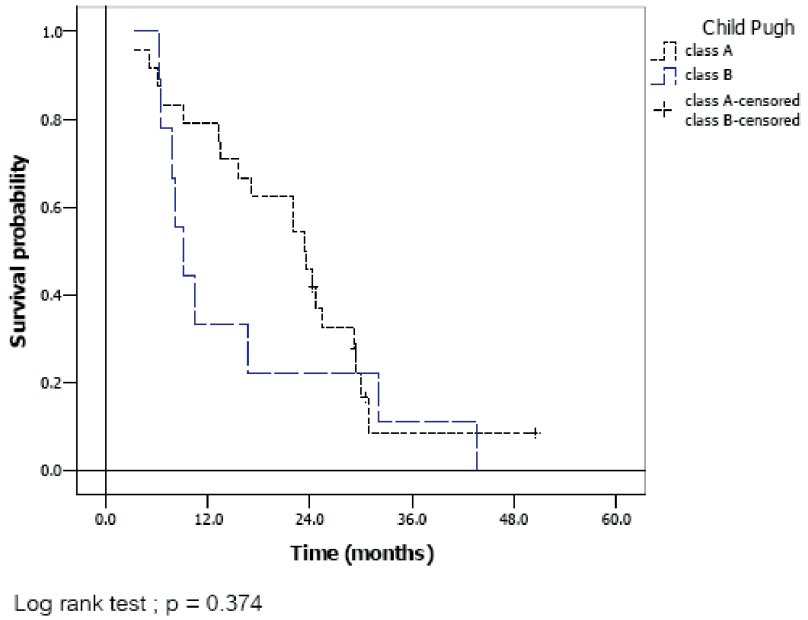
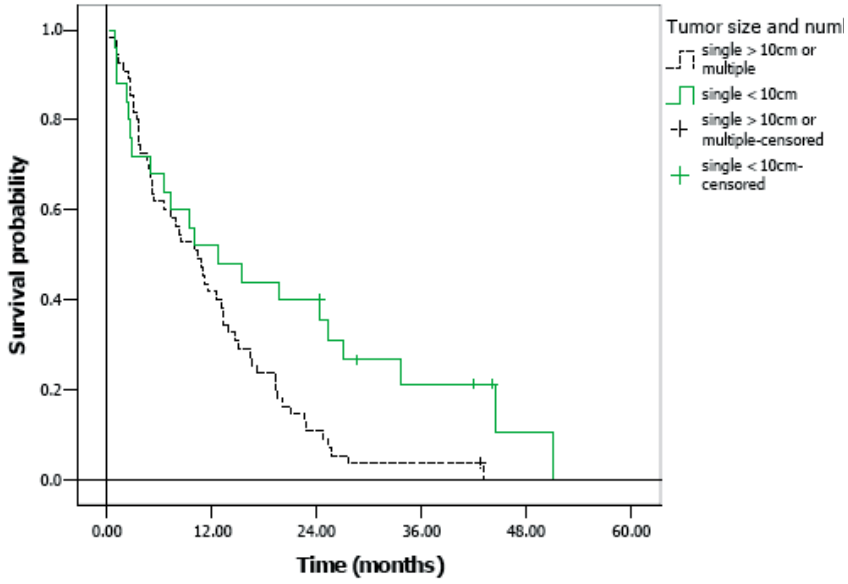


Figure 2 Survival outcome of 33 BCLC stage A HCC patients treated with TACE according to Child Pugh classification.



Log rank test; P = 0.01

Figure 3 Survival outcome of 80 BCLC stage B HCC patients treated with TACE according to the tumor size and number.

Table 3 Univariate Analysis of Prognostic Variables for Survival

Characterisitics	No. of patients	Probability of Survival (%)		P
		1 year	2 years	
Sex				
Men	121	45	22	0.541
Women	23	35	17	
Age (yr)				
≤50	40	40	10	0.150
>50	104	44	25	
HbsAg				
Positive	83	40	21	0.810
Negative	61	48	21	
Tumor number				
Single	96	46	25	0.056
Multiple	48	35	13	
Albumin (g/dl)				
>3.8	98	54	17	0.100
≥3.8	46	38	28	
Total bilirubin (mg/dl)				
≤1.0	68	47	22	0.415
>1.0	75	40	20	
Prothrombin time (INR)				
≤1.1	90	47	22	0.400
>1.1	54	37	19	
Child-Pugh class				
A	106	49	23	0.095
B	38	26	16	

percutaneous ablation or the shortage of organ donors. Thus, these patients are usually treated by various palliative therapies, mostly TACE. The one and two years survival rate of the BCLC stage A patients from our study were 66% and 39% respectively. It is difficult to compare the efficacy of TACE in these patients with one who received only conservative treatment because the chance of tumor response and prolong survival. Data from Japan showed the one and two years survival rate were 43.9% and 12.8% respectively in the 17 HCC patients smaller than 5 cm who received conservative treatment.[8] Another study from Italy show the one and two years survival rate were at 81% and 55%, respectively in the 39 early stage HCC patients.[20] Although the data came from different population and showed the difference outcome on conservative treatment, TACE seems to show survival benefit in the BCLC stage A patients especially those with Child-Pugh class A according to the result from our study. However, because of the small numbers (N = 9) in Child Pugh class B and the 2 years survival rate did not significantly different form Child-Pugh class A, further investigation are need to show the benefit of TACE in the early stage HCC and Child-Pugh class B patients.

In regarding to the BCLC stage B patients, which contained the group of tumor size larger than 5 cm or multiple tumors, there is still some different outcome of those who have single tumor ≤10 cm with those who have single tumor >10 cm or multiple tumors. The

result from our study showed the promising outcome of 1 and 2 years survival rate (52% and 40%,respectively) in those who have single tumor ≤10 cm. Thus, TACE seem to show the survival benefit in the BCLC stage B patients with single tumor >10 cm.

This study was the first study which demonstrate the efficacy of the combination chemotherapeutic agents used in TACE according to the BCLC staging system. Further investigations especially randomized controlled trials are needed to demonstrate the efficacy of combination chemotherapeutic agents used in TACE with single chemotherapeutic agent or different regimens.

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