Original Article

Transarterial chemoembolization in patients with hepatocellular carcinoma beyond Barcelona-Clinic Liver Cancer- B and portal vein tumor thrombosis: Experience from a tertiary care center

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Abstract

Background: Transarterial chemoembolization (TACE) is the preferred treatment for patients with intermediate-stage hepatocellular carcinoma (HCC) without portal vein tumor thrombosis (PVTT). However, select patients with advanced HCC and with PVTT have shown improved survival with TACE. This study was undertaken to evaluate the outcome of TACE in patients with HCC beyond Barcelona-Clinic Liver Cancer- B (BCLC - B) and those with HCC and PVTT.

Methods: Patients with unresectable HCC, subjected to TACE were included. HCC patients with PVTT involving main portal vein and, poor performance status were excluded from the study. Patients were stratified according to performance status, alpha feto protein (AFP) values, and up-to-seven criteria. Individually and using various combinations, the influence of these variables on survival was also estimated.

Results: A total of 50 patients were included in the study. PVTT was present in 12 patients. Clinically, significant liver failure was observed in two patients. The average overall survival of patients beyond BCLC-B following TACE was 13 months. Survival was not influenced by tumor invasion into the portal vein. Patients with higher AFP levels had comparable survival provided their tumor load was satisfying up-to-seven criteria.

Conclusion: We conclude that TACE could improve survival in selective HCC patients beyond BCLC-B and with PVTT not extending to the main portal vein.

Keywords:
Hepatocellular carcinoma, portal vein tumor thrombosis, transarterial chemoembolization, up-to-seven criteria

Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver and nearly 80% of cases and deaths occur in the developing countries.[1,2]

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In developing countries, due to lack of mandatory vaccination against the hepatitis B virus and the absence of standard surveillance protocol for HCC in cirrhotics, patients present at advanced stages. With the limited option for a cure at this stage, palliative therapies like transarterial chemoembolization (TACE) and sorafenib are most commonly employed.[3]

Barcelona Clinic Liver Cancer (BCLC) classifies HCC according to tumor characteristics, degree of cirrhosis, and performance status of patients and recommends stage-based treatment. Due to the stringent selection criteria of BCLC, many patients with HCC will be subjected to the best palliative care only. However, a few select patients beyond BCLC-B have been shown to have improved survival following TACE.[4,5]

HCC with portal vein tumor thrombus (PVTT) is generally considered to be advanced and TACE is not recommended routinely. Transarterial radioembolization (TARE) is the treatment of choice for PVTT but is very expensive and not easily available. A positive response of tumors in HCC with PVTT following TACE has also been reported.[6]

This study was undertaken to evaluate the outcome of TACE in patients with HCC beyond BCLC-B and those with HCC and PVTT.

Materials and Methods

This was a retrospective analysis from a prospectively collected database of all HCC patients, who were treated in our department from February 2012 to July 2017. The data was obtained from the project approved by the institutional ethics committee (IEC) for HCC patients undergoing TACE in our institution. Patients underwent blood investigations including liver function test, alpha-fetoprotein (AFP), and screening for hepatitis B and C. An upper gastrointestinal endoscopy was done to assess gastroesophageal varices. Multidetector four-phase contrast-enhanced computer tomography (CECT) (Siemens Somatom 64 slice CT; Version 2009) and/or magnetic resonance imaging (MRI) (Siemens MagnetomAvento1.5 Tesla; Version 2009) was done and diagnosis of HCC was arrived according to European Association for Study of Liver (EASL) criteria.[7] Performance status (PS) of patients was scaled according to the Eastern Cooperative Oncology Group (ECOG) scoring system.

In this study, we selected the patients with HCC undergoing TACE fulfilling the following inclusion criteria: patients with HCC beyond BCLC-B associated child's A or B cirrhosis, less than 50% involvement of liver by HCC, HCC with PVTT up to the involvement of the right and left but not involving main portal vein; patients with ECOG PS 0–2 and patients willing for therapy and follow-up. Patients having a severe comorbid illness, extrahepatic disease, biliary obstruction, and previous history of decompensation were excluded from the study.

A transfemoral route was preferred for TACE. After celiac and superior mesenteric angiogram, the artery supplying tumor was identified and selective cannulated using 2.7 F Progreat microcatheter. The chemotherapeutic drugs used include 50 mg of doxorubicin and 10 mg of mitomycin C. Following injection of the drugs selectively to the tumor, this tumor feeding artery was embolized with either polyvinyl alcohol (PVA) particles or Gelfoam.

Patients were followed up at 1, 3, 6, and 12 months or till death. During each follow-up visit, patients were subjected to clinical examination, serum AFP estimation, and either CECT or MRI. The response to TACE was assessed according to modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria.[8] Those with stable disease or with partial response were subjected to another session of TACE provided they fulfill other inclusion criteria. Patients with progressive disease were provided with the best supportive care. Beyond 12 months, follow-up was done annually or till their death.

Data analysis was performed using Statistical Package for the Social Sciences (SPSS) software (version 18.0). Categorical data were expressed as proportions and continuous variables as mean with standard deviation or median with range. Univariate analysis was done to identify factors that may influence the survival of patients. Patients were stratified into various groups according to performance status, AFP values (with cut-off of 400 ng/mL), up-to-seven criteria beyond Milan criteria. Individually and using various combinations, the influence of these variables on survival was also estimated. Survival analysis was done using Kaplan-Meier analysis and the log-rank test was used to find differences among various groups.

Results

A total of 150 patients of HCC were treated during the study period. TACE was offered to 63 patients, out of which 13 patients did not fulfill the inclusion criteria and were excluded; therefore, only 50 patients were included in this study. These 50 patients underwent 58 sessions of TACE. The basic demographic and tumor characteristics of patients are displayed in Table 1.

Hepatitis B and C virus infection was found in 13 (26%) and 6 (12%) of the patients respectively. AFP level was less than 400 ng/mL in 32 (64%) of the patients.

Key Message

Our study of patients with hepatocellular carcinoma showed a subset of stage B in Barcelona cancer liver clinic (BCLC) system with prolonged survival following trans-arterial chemoembolization, though the latter was not recommended for this group of patients with portal vein tumor thrombus in the original BCLC guidelines.

Up-to-seven criteria were fulfilled by 10 patients only. Solitary HCC was found in 28 (56%) patients and the mean tumor size was 8.73 cm (range-1.7–20 cm).HCC with PVTT was present in 12 (24%) patients.

The most common complication following TACE was post-embolization syndrome characterized by self-limiting vomiting 35 (70%), abdominal pain 20 (40%), and fever 17 (35%). Around 95% of patients had a transient rise in transaminase levels and two patients had a hepatic failure.

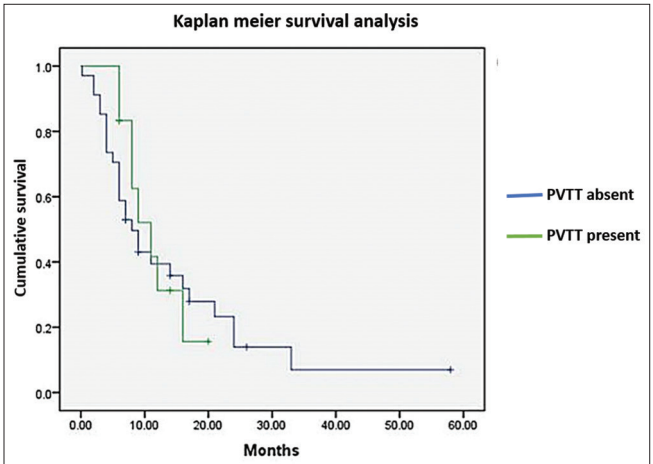
The mean follow-up duration of the patients was 11 (1–58) months. During this period, 39 patients died and four patients were lost to follow-up. The survival of patients for 6 months, 1, and 2-year were 59%, 34%, and 21%, respectively. The average survival of our HCC patients beyond BCLC- B undergoing TACE is 13 ± 2 months. The local outcome following TACE was as follows: (i) complete response- 1 (2%) patient; (ii) partial response-10 (20%) patients; (iii) stable disease or progressive disease- 35 (70%) patients.

The effect of various variables on the survival of patients undergoing TACE was analyzed and is displayed in

Table 1: Demographic and tumor characteristics of hepatocellular carcinoma (HCC) patients (n=50)

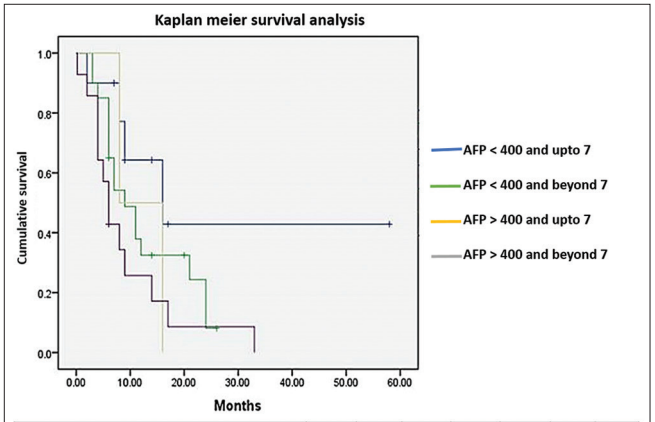
Variable		Frequency *(n=50)* (%)
Age (years) (mean ± SD)		58.12 ± 15.7
Sex	Men	36 (72%)
	Women	14 (28%)
Etiology	Alcohol	13 (26%)
	HBV	13 (26%)
	HCV	6 (12%)
	Others	16 (32%)
CTP class	A	33 (66%)
	B	17 (34%)
AFP (ng/mL)	<400	32 (64%)
	>400	18 (36%)
Number of lesions	Solitary	28 (56%)
	Multiple	22 (44%)
Up-to-7	Within 7	10 (20%)
	Beyond 7	40 (80%)
PV thrombosis	Present	12 (24%)
	Absent	38 (76%)

HBV= Hepatitis B Virus, HCV= Hepatitis C Virus, CTP= Child-Turcotte-Pugh, AFP= Alpha Feto Protein, PV= Portal vein, SD = Standard deviation



Survival in months	0	10	20	30	40	50	60
Patients with PVTT absent	38	18	10	3	1	1	0
Patients with PVTT present	12	5	2	0	0	0	0

Figure 1: Survival curves of influence of hepatocellular carcinoma (HCC) with portal vein tumor thrombus (PVTT) in patients undergoing transarterial chemoembolization (TACE)



Survival in months	0	10	20	30	40	50	60
Patients with AFP <400 and upto 7	7	5	3	2	2	2	2
Patients with AFP <400 and beyond 7	21	11	8	0	0	0	0
Patients with AFP >400 and upto 7	2	1	0	0	0	0	0
Patients with AFP >400 and beyond 7	15	5	2	2	0	0	0

Figure 2: Subgroup analysis of the combined influence of alpha-fetoprotein (AFP) and up-to-seven criteria on the survival of hepatocellular carcinoma (HCC) patients undergoing transarterial chemoembolization (TACE)

Table 2: Details of various factors and its influence on survival as shown by analysis in patients of hepatocellular carcinoma (HCC) (n=50) undergoing transarterial chemoembolization (TACE)

Variable		Survival (months) mean ± S.D	Hazard Ratio (95% CI)	*P*
Gender	Men	12.3 ± 1.9	0.525 (0.239-1.15)	0.107
	Women	18.3 ± 5.4		
ECOG PS	0,1	18.1 ± 3.4	0.298 (0.136-0.654)	**0.003**
	≥2	7.1 ± 1.2		
CHILD status	A	13.25± 1.93	0.534 (0.234-1.218)	0.136
	B	10.49 ± 3.67		
AFP	≤400	18.58 ± 4	0.497 (0.249-0.994)	**0.048**
	>400	9.5 ± 2.2		
Up-to-7	In	23.8 ± 7.7	0.238 (0.078-0.733)	**0.012**
	Out	12 ± 1.7		
PV Thrombosis	Present	14.7 ± 2.9	0.885 (0.399-1.964)	0.764
	Absent	11.6 ± 1.5		

ECOG= Eastern Cooperative Oncology Group, PS= Performance Status, AFP= Alpha Feto Protein, PV= Portal Vein, CI= Confidence Interval, SD= Standard Deviation

Table 3: Subgroup analysis of the combined influence of alpha-fetoprotein (AFP) and up-to-seven criteria on the survival of hepatocellular carcinoma (HCC) patients undergoing transarterial chemoembolization (TACE)

Variable		Survival (months) Mean ± S.D	Hazard Ratio (95% CI)	*P*
AFP and Up-to-7	AFP ≤400 Up-to-7	30.7 ± 9.6		
	AFP ≤400 Beyond 7	12.5 ± 1.9	0.357 (0.118-1.08)	0.173
	AFP >400 Up-to-7	12 ± 4	0.718 (0.359-1.438)	0.408
	AFP >400 Beyond 7	9.2 ± 2.5	0.717 (0.162-3.177)	0.019

CI= Confidence Interval, SD= Standard Deviation

Table 2. AFP level greater than 400 ng/mL, ECOG performance status of 2 or more, and up-to-seven criteria were the factors that showed significant association with the mortality. CHILD class (A or B), gender, and presence of PVTT did not significantly influence survival. Figure 1 depicts comparable survival between HCC with and without PVTT in our patients.

By combining variables, patients were stratified into various subgroups to identify the significance of survival in specific subgroups. A subgroup of patients with AFP levels >400 ng/mL and tumor load satisfying up-to-seven criteria still had a comparable survival with those who had low AFP levels as depicted in Figure 2 and Table 3.

Discussion

HCC presents at a later stage with large or multifocal tumors in developing countries. Most of them are beyond the scope of resection, transplantation, or any other ablative therapies.[3] TACE is the most common palliative treatment for locally advanced HCC. Though BCLC staging categorizes treatment of HCC patients holistically, few patients who would benefit particular treatment are denied of it due to stringent inclusion criteria followed by the staging system. Most of the studies regarding TACE in HCC had dealt with small tumors and its outcome in large tumors and patients falling beyond BCLC- B is not analyzed widely.[9]

Super-selective TACE is a safe procedure and most of our patients did not have any major complications following it. Even though we provided TACE for patients beyond BCLC- B and those with PVTT, the post-procedure morbidity was comparable to that following TACE as reported in BCLC- B patients.[10] Although two of our patients had a hepatic failure, they recovered with supportive treatment. None of our patients had acute kidney injury or liver abscess as mentioned in other reports.

About 30% of our patients had either partial or complete response. Tumor response to TACE is variable in literature ranging from 17–62%. The overall survival following TACE in our patient was 13 months. This was less in comparison with the earlier studies.[3,11] This could be since most of the studies have been done in BCLC-B patients and our patients had more advanced disease. Our survival rate is comparable if studies done on patients with advanced HCC alone are considered.

HCC with PVTT has been considered as a contraindication for TACE. Factors like arterio-portal shunting interfering with the drug deposition and high-

risk of liver failure due to compromised blood flow have been implicated as a cause for poor response and toxicity following TACE in PVTT. None of our 14 patients with PVTT restricted to the right or left portal vein had post-procedure complications. This could be due to the super-selective embolization done.[12,13] In a meta-analysis by Xue *et al*., it was concluded that the 6-month survival of patients with PVTT improved significantly following TACE.[14] In our study, there was no significant difference in survival between those who had PVTT and those who lacked any portal vein invasion. Besides, there was better survival of this subgroup with PVTT when compared to other studies.[15,16]

Tumor biology determines the outcome of the disease. AFP levels and tumor size which are considered surrogate markers of the biology of the tumor.[9,17] However, in our study, AFP levels were correlating with survival significantly when compared to tumor size and vascular invasion. Further, subgroup analysis of various combinations of these surrogate markers revealed that even patients with less AFP levels have a favorable outcome to TACE. Besides, a particular subgroup with higher AFP levels, but less tumor load also have a comparable outcome with less AFP subgroup. This may provide an opportunity for selecting only a particular group of patients with favorable biology and treat only these patients. This could result in a better outcome of TACE in good biology patients and avoiding TACE and its complications in those with poor tumor biology.

We have certain limitations in the study. It is a retrospective study involving a smaller group of patients. In developing countries, where resources and facilities are limited and most of the advanced HCC patients are approached with nihilism, TACE in a select group of patients can still provide an improved survival.

To conclude, TACE could provide an improved survival in selective HCC patients beyond BCLC-B. AFP levels and performance status of patients predicted survival in our patients. PVTT not extending to the main portal vein is not a contraindication for TACE.

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Conflicts of interest
There are no conflicts of interest.

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