ORIGINAL ARTICLE

OUTCOME OF TRANS ARTERIAL CHEMO EMBOLIZATION (TACE) IN PATIENTS WITH UNRESECTABLE HEPATOCELLULAR CARCINOMA IN A SUBSET OF PAKISTANI POPULATION

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ABSTRACT

PURPOSE: To evaluate the outcome following transarterial chemoembolization (TACE) in patients with unresectable hepatocellular carcinoma (HCC) secondary to hepatitis B/C in a subset of Pakistani population. **SUBJECT AND METHODS:** After approval of institutional ethical review committee a prospective study of 81 patients having chronic liver disease secondary to Hepatitis B/C presented with unresectable HCC that referred to the department of interventional radiology of our hospital between January 2012 and December 2013 for TACE. The average age of the patients was 45.05 ± 7.47 years. Out of 81 cases, 40 (49.39%) were male and 41 (50.62%) were female. 64.2% of patients had two tumors and 35.8% had single tumors. Hepatitis B infection was the most common etiological factor of HCC, seen in 59 (72.83%) patients. Regarding the type of Child Pugh's classification, class A was observed in 49.38% patients and class B was observed in 50.52%. Single TACE was performed in 46 (56.79%) patients and twice in 35 (43.21%) cases. 35 (43.20%) patients have normal values (<20 ng/ml) of AFP. **RESULTS:** Response of TACE by using triphasic CT imaging in the patients of HCC is complete reduction was observed in 9.08% cases, partial reduction was 58.82% while in 32.1% cases disease was stable. According to operational definition of the study, satisfactory response was observed in 56.79% (46/81). Rate of satisfactory outcome was high in single tumor treatment as compare to multiple tumors (75.9% vs. 46.2%; 0.01). The overall survival rates at 1 and 2 years were 65% and 45%, respectively. Post TACE complications were recorded as postembolization syndrome, deranged renal parameters and hepatic failure in 17.28%, 14.8% and 4.8% respectively. **CONCLUSION:** TACE has been used extensively in the palliative treatment of unresectable HCC. In our study TACE showed favorable local outcome and the survival rates were comparable with those reported by other international studies.

Keywords: Hepatocellular carcinoma, survival rate, transarterial chemoembolisation

Introduction

Hepatocellular Carcinoma (HCC) is cancer of epithelial origin arising from hepatocytes, accounting for 80% of all primary liver cancer.[1] HCC ranks fifth among the most common cancers worldwide and represents the third most frequent cause of cancer-related mortality.[2] The incidence of HCC is high in the developing countries especially the Sub-Saharan Africa & South East Asia. In Pakistan prevalence of HCC varies from 3.7% of all malignant tumors to 16%. Epidemiological and experimental studies have demonstrated a convincing role of chronic infection with hepatitis B (HBV) and hepatitis C (HCV) on a background of cirrhosis as major risk factors for the development of hepatocellular carcinoma. In Pakistan carrier rates for HBsAg and hepatitis C are reported to be 10-16% and 2-6% respectively. These figures

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are alarmingly high and stress the need for epidemiological studies to better delineate the relative roles of these two potentially carcinogenic viruses in the etiology of hepatocellular carcinoma in our population.[3] Known risk factors for HCC include chronic viral hepatitis, cirrhosis, heavy alcoholism, non-alcoholic fatty liver disease and certain inherited metabolic conditions such as hemochromatosis and alpha-1-antitrypsin deficiency.[4] Although surgical resection offers a better curative option than nonsur-gical treatment, approximately 70% to 80% of cases are inoperable because of associated liver cirrhosis or advanced disease at the time of presentation. Transarterial chemoembolization (TACE) has been widely used for the management of unresectable HCC.[5]

TACE has evolved over the last two decades as an effective - and the most widely used - palliative treatment for unresectable HCC. There are a number of published studies on the efficacy of TACE, including randomized control trials comparing its outcome with supportive therapy. However, most of these are from the developed countries.[6] There is paucity of information on the outcome of HCC patients treated with TACE in our country. This study was designed to estimate the success rate and is possibly the first study on TACE in Pakistan.

Material and Methods

After approval of institutional ethical review committee and after written informed consent from all participants, consecutive HCC patients were included that referred to the department of interventional radiology of our hospital between January 2012 and December 2013. Complete blood count (CBC), liver function tests (LFT) and serum alpha-fetoprotein (AFP) were checked in each patient. Patients were classified into Child's A, B or C based on the Child-Pugh classification.[7] Abdominal ultrasound (USG) and triphasic CT of the liver were performed in each patient.

Diagnosis of HCC, requires either (a) fine needle aspiration cytology (FNAC) or (b) AFP more than 300 ng/ml and arterialization of the mass on contrast-enhanced MDCT. HCC patients 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, who were unsuitable for ablative therapy or surgery, were also included. Patients with extra hepatic disease; coagulopathy; biliary obstruction; comorbid illness like coronary artery disease, congestive heart failure, chronic kidney failure were excluded from this study.

TACE was performed through the transfemoral route. Initially SMA and celiac axis arteriogram were obtained. Selective cannulation of the hepatic artery supplying the lesion was performed using a 5F celiac catheter and a 0.035-inch J-tip Terumo guidewire. Further, the catheter was placed as close as possible to the lesion using a 3F microcatheter. The chemotherapeutic drug emulsion was prepared. This consisted of epirubicin 50 mg, 3 ml of iodinated non-ionic contrast media and 5 ml of iodized oil (lipiodol). The chemotherapeutic drug emulsion was then delivered through this cannulated feeding hepatic artery. The amount of emulsion to be injected was decided during the procedure. When the lesion showed complete coverage with lipiodol or if there was reflux of emulsion into normal branches, further injection of emulsion was stopped. The amount of emulsion injected varied from case to case. Subsequent to the injection of the emulsion, this feeding artery was embolized using 250-300 micrograms PVA particles. We used a microcatheter-coaxial system to access small and tortuous feeders. Follow-up after TACE included a thorough clinical examination; serum AFP estimation (if more than 20 ng/ml at enrollment); and MDCT at 1.5, 3, and 6 months to assess response. If all clinical and biochemical parameters were normal at 6 months following treatment, then CT was done at yearly intervals. The main outcome variable of interest was the local tumor response to TACE as estimated on the basis of MDCT. The tumor response was classified as: complete reduction, partial reduction and stable disease. These entities were defined as follows: (a) complete reduction - when the tumor was fully covered with lipiodol and had no enhancing viable tissue; (b) partial reduction - is at least a 30% decrease in the sum of diameters of the viable portion of the (contrast enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions; (c) progressive disease is an increase

of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded or interval development of a new lesion since the treatment started; (d) stable disease is any case that does not qualify for classification as either a PR or progressive disease. TACE was repeated maximum up to 3 times if no reduction is size obtained after that their response was evaluated.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) version 22.0 was used for the statistical analysis. Qualitative variables in frequencies and percentage i-e gender, no of tumors, Child Pugh score, no of times procedure performed and outcome variables i.e. satisfactory response (Yes/ No).

Stratification was done on age, gender, presenting symptoms, no of tumors, normal and abnormal AFP values and Child Pugh scoring to see the effect of these on its outcome by using chi-square test and p value ≤ 0.05 was considered as significant. Survival analysis was estimated using Kaplan-Meir analysis method. Post TACE complications were also recorded.

Results

A total of 86 patients were initially included in this study. TACE could not be performed in five patients due to coagulopathy in 2 patients, concomitant renal failure in 2 patients and technically difficult TACE due to non-cannulation of hepatic artery in 1 patient. The remaining 81 patients were successfully subjected to a total of 116 sessions of TACE (one session in 46 patients and two sessions in 35 patients).

The average age of the patients was 45.05 ± 7.47 years (Tab. 1). Out of 81 cases, 40 (49.39%) were male and 41 (50.62%) were female. Patients were grouped according to age and symptoms at the time of presentation. (Fig. 1 and 2) 15 patients were asymptomatic at presentation, the majority having a constitution of symptoms at presentation. The symptoms included right upper quadrant pain in 25 (30.8%), weight loss in 40 (49.3%), anorexia in 30 (37.0%), and abdominal distension in 18 (22.2%) patients. Hepatitis B infection was the most common etiological factor of HCC, seen in 59 (72.83%) patients (Fig. 3). Thirty one patients (38.20%) had tumors of size

		Age (Years)	Duration of disease (months)
Mean		45.05	4.30
95% Confidence Interval for Mean	Lower Bound	43.40	4.10
	Upper Bound	46.70	4.49
Median		45	4
Std. Deviation		7.47	.872
Minimum		31	3
Maximum		60	6
Inter quartile Range		13	1

Table 1: Descriptive statistics of study patients (n=81)

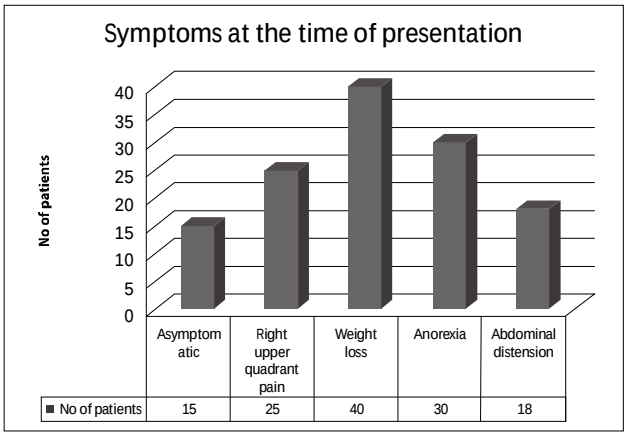

Figure 1: Bar chart shows groups according to patient's symptoms at the time of presentation.

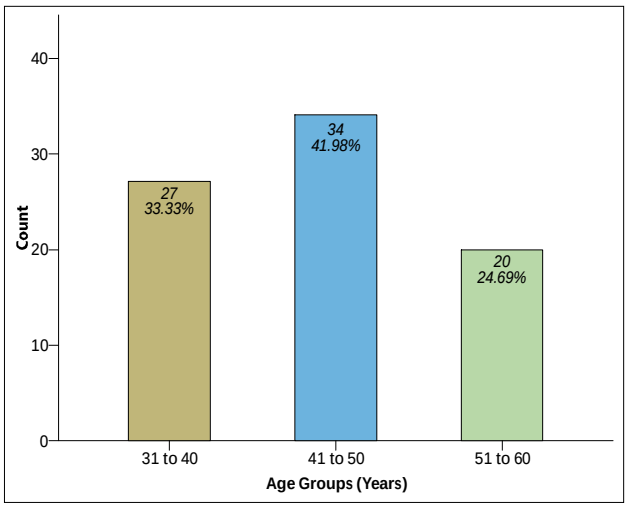

Figure 2: Bar chart shows age distribution of the patients n=81

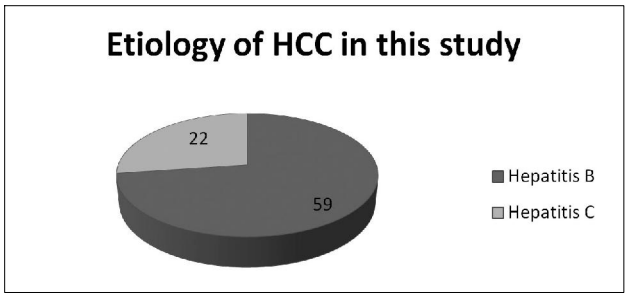

Figure 3: Pie chart shows etiological factor of HCC in this study

≤ 5 cm, 29 (35.80%) had tumors of > 5–10 cm size, and 21 (25.92%) had tumors of > 10 cm size (Fig. 4). Regarding the type of Child Pugh's classification, class A was observed in 49.38% patients and class B was observed in 50.52%. 64.2% of the patients had two tumors and 35.8% had single tumors. The

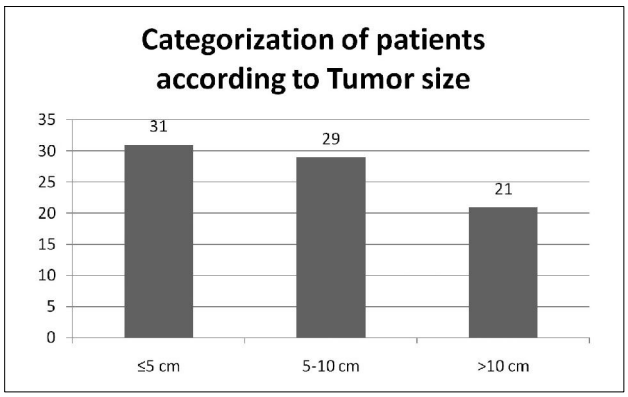

Figure 4: Bar chart shows groups of patients according to the size of tumor.

mean tumor size was 7.59 ± 3.79 cm (range: 1-18 cm). Single TACE was performed in 46 (56.79%) patients and twice in 35 (43.21%) cases as shown in (Fig. 5). 35 (43.20%) patients have normal values (<20 ng/ml) of AFP. (Tab. 2)

Response of TACE by using triphasic CT imaging in patients of HCC was complete reduction was observed in 9.08% cases, partial reduction was 58.82% while in 32.1% cases disease was stable. According to operational definition of study, satisfactory response was observed in 56.79% (46/81) cases as shown in (Fig. 6).

Stratification analysis was performed and observed that satisfactory outcome was not significant among different age groups (0.066). Similarly satisfactory outcome was also not significant between male and

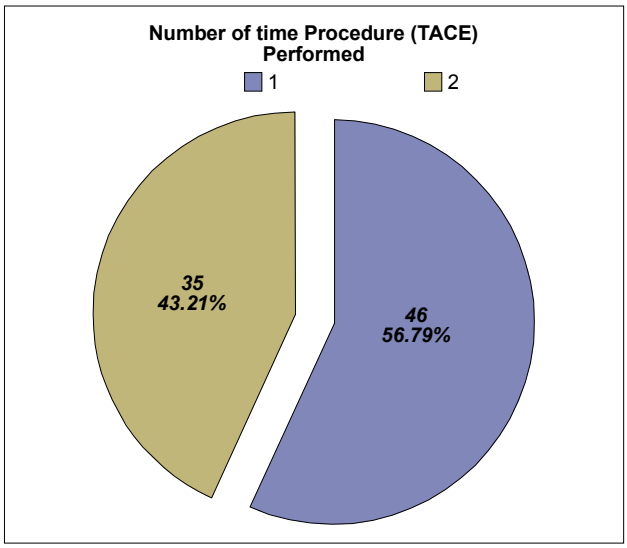

Figure 5: Pie chart shows number of time procedure performed

AFP value	No of patients	Percentages
<20 ng/ml	35	43.20%
>20 ng/ml	46	56.80%

Table 2: Patient's classification according to AFP values

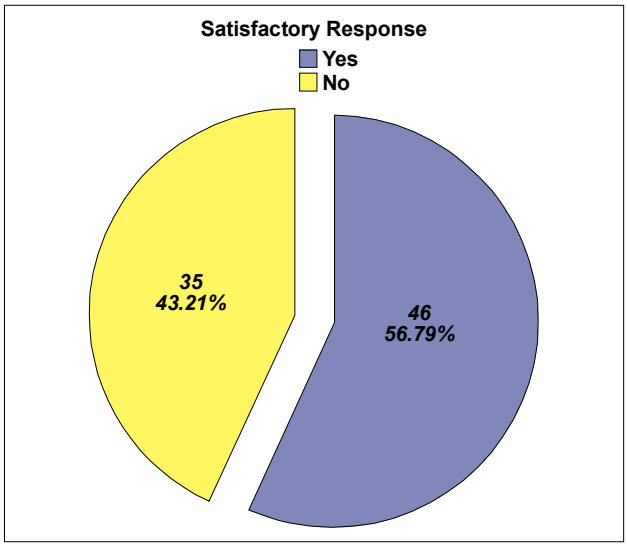

Figure 6: Satisfactory response of tace by using triphasic ct imaging in the patients of HCC

female. Rate of satisfactory outcome was high in single tumor treatment as compare to multiple tumors (75.9% vs. 46.2%; 0.01). Response was also observed with respect to Child Pugh class and duration of disease but no significant effect was observed. (Tab. 3)

Age Groups (Years)	Satisfactory Response		Total	Chi-Square= 806 p=0.066
	Yes n=46	No n=35		
31 to 40 Years	17(63%)	10(37%)	27	
41 to 50 Years	19(55.9%)	15(44.1%)	34	
51 to 60 Years	10(50%)	10(50%)	20	
Gender				
Male	22(55%)	18(45%)	40	Chi-Square= 0.103 p=0.74
Female	24(58.5%)	17(41.5%)	41	
Number of Tumors				
1	22(75.9%)	7(24.1%)	29	Chi-Square= 6.69 p=0.01
2	24(46.2%)	28(53.8%)	52	
Child Pugh Class				
A	23(57.5%)	17(42.5%)	40	Chi-Square= 0.016 p=0.89
B	23(56.1%)	18(43.9%)	41	
Duration of Disease				
3 to 4 months	27(55.1%)	22(44.9%)	49	Chi-Square= 144; p=0.704
5 to 6 months	19(59.4%)	13(40.6%)	32	

Table 3: Satisfactory response of tace procedure by using triphasic CT imaging in the patients of HCC with respect to age groups, gender, no of tumor, child pugh class and duration of disease

Non significant complications were encountered during the procedure and the post procedure complications were mild. Postembolization syndrome was the most common complication in 14 (17.28%), which consisted of pain abdomen, fever, nausea, and vomiting. Deranged renal parameters in 12 (14.8%) patients and hepatic failure in 4 (4.9%) subjects were also encountered. (Tab. 4)

Complications	No of patients	Percentages
Post embolization syndrome	14	17.28%
Derranged renal parameters	12	14.28%
Hepatic failure	4	4.9%

Table 4: Post TACE complications

Patients were followed up for a mean period of 24 months. A total of 27 patients died, while remaining 58 patients were alive at the end of study. Survival data of 73 patients (8 patients died in 1st Year) were used for the Kaplan-Meir survival analysis. The overall survival rates at 1 and 2 years were 65% and 45%, respectively. (Tab. 5)

Mean period follow-up	24 months	
Patient died	1st year	9
	2nd year	18
Survival analysis of 73 patients	1st year	65%
	2nd year	45%

Table 5: Survival analysis using Kaplan Meir analysis

Discussion

Transarterial chemoembolization (TACE) is the most widely used neo-adjuvant treatment for HCC patients listed for Liver Transplant (LTx). Results of randomized controlled trials and meta-analyses of pooled data for patients with non-resectable HCC show a clear survival benefit after TACE compared with conservative management, and is therefore considered as standard of care in non-resectable HCC.[8] Two studies using TACE for bridging to LTx reported excellent outcomes.[9] Nevertheless, only patients with preserved liver function and asymptomatic multinodular tumors without vascular invasion or extrahepatic spread are eligible for TACE to avoid hepatic failure and severe adverse events.[10] Radiofrequency ablation was not considered because only few heterogenous uncontrolled studies suggested a slightly decrease in drop-out rate in patients treated with RFA before LTx and there is the risk of needle tract metastases. Since HCC is generally considered to be chemoresistant, results of systemic therapy have previously been disappointing. Tumor response rates for single or multiple agent chemotherapy regimens were low without durable remission leading to a 1-year survival between 0% to 30%.[11] Increasing knowledge on the molecular pathogenesis of HCC has lead to the development of molecular targeted therapies. The oral multikinase inhibitor sorafenib (Nexavar®) blocks angiogenesis and cell proliferation in HCC. In patients with advanced HCC, sorafenib has shown a significant improvement in time-to-progression (TTP) and OS. After the drug has now been approved by both, FDA and EMEA, it is the new reference standard treatment of patients with advanced HCC.[12] In this study the average age of the patients was 45.05 ± 7.47 years. Out of 81 cases, 40 (49.39%) were male and 41 (50.62%) were female. 64.2% of the patients had two tumor and 35.8% had single tumors. Regarding the type of Child Pugh's classification, A class was observed in 49.38% patients and 50.52% were in class B. One time procedure was performed in 46 (56.79%) patients and two time procedure were performed in 35 (43.21%) cases in present study. Many investigators have reported their results of tumors treated with TACE, usually using cross-sectional imaging (ultrasonography, CT scan, or magnetic resonance imaging [MRI] scan) to measure tumor size before and after

therapy and using the World Health Organization (WHO) criteria of tumor size to determine the response rate. By these criteria, complete response indicates complete disappearance of the lesion; partial response means reduction of size (the product of two perpendicular diameters) of greater than 50%; minor response means a reduction of 25-50%; and no change means less than 25% increase or decrease in tumor size. Progressive disease indicates a greater than 25% increase in tumor size.[13-15] In this study complete reduction was observed in 9.08% cases, partial reduction was 58.82% while in 32.1% cases disease was stable. According to operational definition of the study, satisfactory response was observed in 56.79% (46/81). The percentage of good response was 70% in the TACE group which is in accordance to the data of many other reports,[16-20] however it was higher than other reports.[21] Meanwhile, it was 60% in the RFA group that was in the agreement with other study.[19] On the other hand, it was 90% in the combined therapy group, and this goes with data of other authors.[22-24] Many potential factors determine a patient's response to TACE.[25,26] One of the more important variables is the degree of cirrhosis and not the tumor itself. Larger tumors at baseline were less likely to respond to TACE.[27] In the current study, 70% of tumors less than 3 cm in diameter responded to TACE compared with only 43% of tumors more than 10 cm in diameter. Katyal et al.[28] reported that HCCs that were predominantly hypervascular at baseline helical arterial phase CT scan were more likely to respond to TACE and that these patients had prolonged survival compared with patients who had less vascular HCCs.

It is noteworthy that patients with hypervascular HCCs have a survival benefit from TACE, even if they are classified as nonresponders by size criteria or our combined criteria. The 12-month, 18-month, and 24-month survival rates for patients classified as hypervascular nonresponders (44%, 17%, and 10%, respectively) compare favorably with historical controls of patients with untreated HCC.[29-30] This has been explained by Peng et al.[21] that occlusion of hepatic arterial flow by means of TACE before RF ablation reduces the cooling effect of hepatic blood flow on thermal coagulation. Furthermore, lipoidol and gelatin sponge particles used in TACE reduce the portal flow around the tumor by filling the peripheral portal veins around the tumor with lipoidol via multiple arterio-portal communications, thus the necrotic area induced by RFA may be increased, in addition to, the positive thermal impact on the anticancer effect of the retained chemotherapeutic agent. While TACE therapy is relatively superior to RFA, one considering the percentage of good response and recurrence free survival that is in accordance with other studies[31-34] which reported that RFA is 100% effective in lesions not more than 3 cm, while TACE is more suitable for larger lesions. Regarding the alpha-fetoprotein, it was decreased gradually near to the normal levels in all patients who developed good response in the three groups, and this goes with data reported by other authors.[31]

Conclusion

In conclusion, TACE is a safe and effective palliative procedure for unresectable hepatoma and may even replace surgical resection in some cases in Pakistan.

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