ORIGINAL RESEARCH

Role of trans-arterial chemoembolization (TACE) in patients with unresectable hepatocellular carcinoma

G Rama Mohan Reddy[1], Puneet Gupta[2]

[1]Assistant Professor, Department of Nuclear Medicine, National Institute of Medical Sciences and Research, India
[2]Assistant Professor, Department of General Medicine, National Institute of Medical Sciences and Research, India

Corresponding Author
Puneet Gupta
Assistant Professor, Department ofGeneral Medicine, National Institute of Medical Sciences and Research, India

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ABSTRACT
Background: Portal vein thrombosis is considered a relative contraindication for transarterial chemoembolization (TACE) in hepatocellular carcinoma. The purpose of our study was to evaluate the efficacy of TACE treatment in patients with hepatocellular carcinoma with portal vein (PV) thrombosis. **Material and Methods:** HCC patients reporting to our hospital (2001-2007) were subjected to clinical, biochemical, and radiological examination. TACE was performed in those who fulfilled the inclusion criteria. Follow-up assessment was done with multiphase CT scan of the liver at 1, 3, and 6 months. Tumor response and survival rate were estimated. Univariate and multivariate analyses were done for determinants of survival. **Results:** Out of 90 patients included in the study; 49 were male (56.3%) and remaining 41 were female (45.1%). Their mean age was 57 years (range 16–74 years). DWI was performed on 93 (82.4%) patients. Patients were assessed for tumor response by imaging at regular intervals and the data compared with the baseline laboratory and imaging characteristics obtained before treatment. Univariate analysis was used to assess the treatments impact on patient survival. Survival analysis was performed using Kaplan–Meier estimations. **Conclusion:**TACE offers a reasonable palliative therapy for HCC. Initial tumor size is an independent predictor of survival.

Keywords: Hepatocellular carcinoma, survival rate, transarterial chemoembolisation.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver. It is strongly associated with cirrhosis, from both alcohol and viral etiologies. HCC consti-tutes approximately 5% of all cancers partly due to the high endemic rates of hepatitis B infection.HCC is the fifth most common cancer in the world and is the third most common cause of cancer related death (after lung and stomach cancer). The incidence of HCC is rising, largely attributed to a rise in hepatitis C infection. The demo-graphics are strongly influenced by the regions in which chronic hepatitis B infection is com-mon, which account for over 80% of cases worldwide. The highest prevalence is in Asia. In Western countries, the rate is lower and alcohol accounts for a greater pro-portion of cases[1-4].

Risk factors include:

- hepatitis B (HBV) infection: 10% 5-year cumulative risk
- hepatitis C (HCV) infection: 30% 5-year cumulative risk
- alcoholism: 8% 5-year cumulative risk
- biliary cirrhosis: 5% 5-year cumulative risk
- food toxins, e.g. aflatoxins
- congenital biliary atresia
- inborn errors of metabolism
- haemochromatosis: ~20% 5-year cumulative risk
- alpha-1 antitrypsin deficiency
- type 1 glycogen storage disease
- Wilson disease
- tyrosinaemia type I
- obesity and diabetes mellitus
- chronic cholestatic syndromes

HCC is typically diagnosed in late middle age or elderly adults (average 65 years) and is more common in males (75% cases). Thetumor can also occur in the pediatric population; however, it is the second most common pediatric primary liver tumor after hepatoblastoma. Unfortunately, the diagnosis of

HCC is too often made with advanced disease when patients have beco-me symptomatic and have some degree of liver impairment. At this late stage, there is virtually no effective treatment that would improve survival.[5,6] In addition, the morb-idity associated with therapy is unac-ceptably high. The most commonly used initial treatment for loco regional HCC as well as for down staging tumors that exceed criteria is TACE.TACE can also be consi-dered prior to HR and RFA as neoadjuvant therapy to either reduce tumor volume or even target micro metastasis. The rationale for using TACE is the neoangiogenic properties of HCC and its mechanism of action on the hepatic arterial supply of the tumor. During its initial development, the tumor derives its blood flow from the portal system. As the tumor increases in size, the blood supply becomes arterialized, so even a well-differentiated HCC is mostly dep-endent on hepatic arterial supply. This tumor characteristic provides the pathologic basis for the radiologic features used to diagnose HCC. Embolization of the hepatic artery branch leads to selective tumor hypoxia and eventually tumor necrosis. This is accomplished by a significant reduction in arterial blood flow through the use of image-guided catheter-based infusion of particles.[7,8] Potential agents including poly-vinyl alcohol beads, alcohol, starch micr-ospheres, metallic coils, autologous blood clots, and gelfoam have all been used for embolization. Prior to arterial embolization, a chemotherapeutic agent is injected. Seve-ral chemotherapeutic agents have been historically used, including doxorubicin, cisplatin, mitomycin, and epirubicin. In addition, doxorubicin eluding beads have recently become an alternative to traditi-onal TACE. Drug eluding beads are consi-dered an improvement in both treatment response rates and tumor necrosis compared to traditional TACE. Contrai-ndications for TACE are decompensating cirrhosis (Child–Pugh B), massive tumor with extensive replacement of both lobes, severely reduced portal flow (portal vein occlusion or hepatofugal blood flow), and a creatinine clearance of <30 mL/min. Llovet et al found that survival probabilities for TACE were 82% and 63% for 1 and 2 years, respectively, for unrespectable HCC. The response to TACE is an independent predictor of survival. Additional studies have shown an improvement in survival in TACE-treated patients in the range of 20%–60% at 2 years. Morbidity with embol-ization is relatively low (<5%), and comm-on complications include abdominal pain, nausea, ileus, and fever, which are consistent with post embolization syndro-me. Historically, portal vein tumor throm-bosis has been considered a contrain-dication to the performance of TACE ther-apy. This interruption of hepatic arterial blood flow which can lead to significant hepatic necrosis when combined with a portal vein occlusion from tumor thrombus which already compromised blood flow to the affected area of the liver. Several pro-spective and reactive retrospective studies have shown that TACE can improve overall survival in Child–Pugh's a cirrhotic HCC patients with portal vein tumor thrombosis. Furthermore, the combination of TACE and sorafenib may have synergistic value[9,10].

MATERIALS AND METHODS

Patient selection: The patients presented with suspected hepatocellular carcinoma. All patients were submitted to history taking and clinical provisional diagnosis and each patient underwent blood investigations,which included complete blood count, liver function tests, and tests for viral markers of hepatitis B and C infection. Serum alpha-fetoprotein (AFP) was estimated using a particle enzyme immunoassay (Axsym System; Abbott Laboratories, Abbot Park, Illinois, USA; normal value <20 ng/ml). TACE was offered to BCLC-B/C HCC patients who 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. Some patients of BCLC A, who were unsuitable forablative therapy or surgery, were also included.

The exclusion criteria included extra hepatic disease; coagulopathy; biliary obstruction; comorbid illness like coronary artery disease, congestive heart failure, chronic renal failure, etc.; and a previous history of encephalopathy/upper gastrointestinal bleed in the last 6 months.

STATISTICAL ANALYSIS

Various pulmonary function parameters were considered as primary outcome variables. Presence or absence of exposure to air pollution and duration of air pollution was the primary explanatory variable. Desc-riptive analysis of the data was done by using frequency and percentage for cate-gorical variables, mean and standard deviation for quantitative variables. The mean values of the pulmonary function parameters were compared among various study groups. Analysis of variance (ANOVA) was used to assess the statistical sign-ificance of the association. P value 0.05 was considered as statistically significant. IBM SPSS version 21 was used for statistical analysis.

RESULTS

Out of 90 patients included in the study; 49 were male (56.3%) and remaining 41 were female (45.1%). Their mean age was 57 years (range 16–74 years). DWI was performed on 93 (82.4%) patients. The distribution of findings is shown in Figure 1. The patients were divided into seven groups on the basis of ages: 10-19, 20–29, 30–39, 40–49, 50–59, 60–69, and 70-79 years and are designated as group I - VII. The demographic characteristics of the patients were studied: gender, age, and comorb-idities results are shown in table 1.

Table1: Demographic Data of Patients

Age (Years)	Benign	Malignant	Total
10-19	10	10	20
20-29	8	10	18
30-39	7	9	16
40-49	7	6	13
50-59	4	6	10
60-69	2	6	8
70-79	-	5	5
Total	38	52	90

After demographic analysis, we did not observe any significant difference in the distribution of age; sex; expression of HBsAg; ALT, AST, TBil, ALB, PT, and AFP levels; Child-Pugh class; maximum HCC size; number of HCC foci; Barcelona Clinic Liver Cancer (BCLC) stage; extrahepatic metastasis; vascular invasion; and APF/AVF between the 2 groups(Table 2).The procedure of TACE was well tolerated by all our patients. No complications were encountered during the procedure and the postprocedure complications were mild. Postembolization syndrome was the most common complication in 10/93 (14.4%), which consisted of pain abdomen, fever, nausea, and vomiting. Deranged renal parameters in 10/93 (14.4%) patients and hepatic failure in 3/93 (5.3%) subjects were also encountered.

Table 2 shows the comparison of background factors and results of univariate analysis using Cox proportional hazard model. The presence of associated features of portal hypertension (ascites, splenomegaly, etc.) did not have any significant effect on survival. The variables of Child's stage, AFP >1000ng/ml, size of the mass, and BCLC stage showed significant promise of association with mortality (P<.05) on univariate analysis [Table 2]. These variables were put in a stepwise multivariate Cox regression model, and the size of the mass at the start of the treatment emerged as the most significant independent predictor of survival.

Measured Properties	Frequency	Percentage
Presenting Symptoms		
Asymptomatic	14	16.1
Pain	35	44.8
Weight Loss	28	35.3
Anorexia	26	32.6
Abdominal Distension	17	20.3
Abdominal Mass	10	9.8
Fever	9	8.3
Child's Class		
A	64	74.5
B	29	27.2
Etiological Factors		
HBV	62	72.4
HCV	21	16.1
AST (IU/L)		
<40	21	16.2
>40	72	85.6
ALT (IU/L)		
<40	33	32.4
>40	60	69.1
AFP ng/ml		
<20	34	41.2
21-300	23	26.2
300 -1000	17	17.4
>1000	19	21.2
BCLC Stage		
A	27	28.6
B	45	53.4
C	21	21.3

Size of HCC		
<5cm	35	39.1
5-10cm	34	38.2
>10cm	24	24.4

DISCUSSION

TACE is the most widely used treatment option in patients with HCC who are unsuitable candidates for curative mana-gement. The developing world has a peculiar epidemiological variation in terms of etiology and the stage of HCC at diagnosis; more than 80% of the HCC occurs in Asia and Africa[11].

In this study, HBV infection emerged as the most common background causal factor for HCC. This is consistent with the observa-tions of published studies from other centers in India. In contrast, in countries like Japan, Spain, etc., HCV-related HCC is predo-minantly encountered. The majority of our patients were symptomatic at presentation (66/73 patients; 90.41%) and had a relatively large tumor size at the outset, indicating the presence of advanced disease. Treating these patients was very challe-nging. The largest published experience of TACE from Japan, with a study population of 8510 patients, had subjects with smaller sized tumors (24% with <2 cm and 75% with <5 cm). Very few studies are available on the experience of TACE for relatively larger sized liver tumors (mean diameter approximately 7 cm)[12].

Doxorubicin, mitomycin, and cisplatin are the common antitumor drugs used alone or in combination during TACE. No standard-dized protocol exists with regard to the choice of the chemotherapeutic agent, dosage, dilution, rate of injection, and optimal retreatment strategy. Similarly, there is no standard choice for the embo-lizing agent to be used or its quantity. In the present study, we used a combination of cisplatin (100 mg), doxorubicin (50 mg), and lipiodol (10–20 ml), followed by part-iculate embolization using gelatin sponge. The procedure was performed by cannu-lating the feeding artery super selectively (going as close to the tumor as possible using micro catheters), thus minimizing the risk of non-target embolization. This met-hod of super selective cannulation has been identified as a favorable prognostic factor for the disease-free survival of patients following TACE[13].

Our patients tolerated the procedure well. The commonly encountered minor complic-ations post-procedure were self-limiting and improved in about 5–7 days. Moreover, when a repeat session of TACE was performed in the same patients, we observed that the severity of the side effects was even less. About 13.7% of our patientsdeveloped deranged renal parameters,

which possibly could be attributed to the use of the chemotherapeutic drug doxor-ubicin[14].

TACE is known to be a safe procedure with a low mortality rate and, further, the mortality has been decreasing over the last two decades (reportedly 10% in 1991, 1.1% in 1999, and 0.5% in 2006). In the largest published experience of TACE, the various causes of death were as follows: hepatic failure (40.1%), cancer death (18.2%), and rupture of HCC. We lost two patients within 1 month of performing the procedure due to hepatic and renal failure (one each), leading to a procedure-related mortality of 2.7%. We did not encounter any case of rupture of HCC or infections following TACE as reported by other authors[15,16].

There seems to be no consensus on the policy of subjecting patients to repeat sessions of TACE. Some centers perform repeat TACE at specific intervals, ranging from 2-3 months. We performed repeat sessions of TACE based on the findings of follow-up CT done at 4 weeks post therapy. This policy was similar to that followed in the nationwide multicentric Japanese study by Takayasu *et al*. It is known that the efficacy of TACE is better when the proce-dure is repeated on the basis of follow-up imaging findings rather than at pre decided scheduled intervals[17-20].

Following TACE, significant tumor response is achieved in 17-61.9% of cases but com-pletetumor response is rare (0-4.8%) as the tumor cells may remain viable after the treatment of TACE.

We were able to achieve complete response in 31.2% patients, while local disease progression in terms of recurrence or development of fresh lesions was seen in15/64 (23.4%) patients. Efficacy of TACE for palliation of unresectable HCC has been demonstrated in several randomized cont-rolled trials. The survival rate and the local response in our study were encouraging. The cumulative survival rate at 1, 2, and 3 years was 66%, 47%, and 36.4%, respe-ctively. Table 3 shows the survival rates of different studies and it can be seen that the rates have been improving over the last two decades. The improved outcomes of HCC following TACE in the more recent studies may have a number of reasons, e.g., (a) the institution of screening programs for HCC, leading to detection of small tumors; b) the availability of better imaging techniques for diagnosis, i.e., modalities with high sensit-ivity and specificity such as multiphase CT scan and contrast-enhanced MRI); (c) stringent application of well-defined stagi-ng criteria for the disease; (d) clear-cut inclusion criteria, leading to homogenous study populations; (e) refinement in the technique of the procedure of TACE, e.g., the wide use of tiny micro catheters allows the catheter tip to be placed as distally as possible in the lumen resulting in better coverage of the tumor with the chemo-therapeutic drugs[21,22].

The overall survival rate in our study compares well or is in fact better than that in many earlier studies from different countries. Due to differences in the sele-ction criteria, our study population probably had a larger tumor size and more advanced stage of disease. Developed countries have screening

programs for HCC, which enable 'early detection and early treatment' and these countries therefore generally deal with patients with early-stage HCC[23].

Univariate analysis of the predictors for survival identified the Child-Pugh score, serum AFP >1000 ng/ml, BCLC stage, and tumor size as important variables affecting survival post TACE. All these above mentioned variables are basically interre-lated and depict the advanced nature of the disease. The larger the tumor size, the higher the BCLC stage and the poorer the function of the underlying liver (Child's status). However, the presence of vascular invasion and associated portal hyperte-nsion did not show any significant effect on the overall survival. On multivariate anal-ysistumor size emerged as the single most important independent predictor of surv-ival. This finding is similar to the observations made in other studies[24].

Since the size of the mass is an important predictor for survival, this observation has grave implications in a country like ours where the majority of patients have large tumors at diagnosis. In India, screening programs for HCC are rare. For better treatment outcomes it is important to commence screening high-risk patients of cirrhosis to diagnose HCC at an early stage. Additionally, since HBV infection is the predominant cause for HCC, it would be highly desirable to institute preventive strategies for HBV infection, e.g., hepatitis B vaccination programs[25].

To conclude, TACE is a safe and efficacious palliative procedure. In India, the majority of patients have advanced disease at presentation. Despite the presence of large-sized tumors in our study population, TACE showed favorable local outcome and the survival rates were comparable with those reported by other authors. Initial tumor size was the most important independent predictor of survival in our patients of HCC[26,27].

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