Original Article

Impact of Transarterial Chemoembolization on 1 year survival rate of Patients suffering from Non-resectable Hepatocellular Carcinoma

1. Amaila Ramzan 2. Hamid Majeed 3. Muhammad Ramzan 4. Saman Chaudhary

1. Resident Doctor, Shoukat Khanum Cancer Hospital & Research Centre, Lahore 2. Asstt. Prof., Sharif Medical & Dental College, Lahore 3. Asstt. Prof. of Radiology, Sheikh Zayed Hospital, Lahore 4. Resident Doctor, Shoukat Khanum Cancer Hospital & Research Centre, Lahore

ABSTRACT

Objective: Treatment of nonresectable HCC remains unsatisfactory and different therapeutic regimes have been tested. Transarterial chemoembolization (TACE) is the most promising palliative modality for unresectable HCC and determination of the survival rates of patients after TACE is important to guide clinicians for proper management of advanced HCC. So objective of our study was to determine 1 year survival rate in patients with unresectable HCC treated by TACE.

Study Design: Retrospective Study.

Place and Duration of Study: This study was conducted at Shaukat Khanum Cancer Hospital & Research Centre, Lahore from July 2009 to June 2010.

Materials and Methods: 90 patients with unresectable HCC who underwent TACE treatment were identified from a prospectively collected database. Patient survival from the first TACE session was calculated at 6 and 12 months duration after TACE, with Kaplan-Meier analysis.

Results: A total of 90 patients were studied. All patients underwent TACE with appropriate technical measures. The age range of patients was 34 years to 84 years. Mean age of patients was calculated to be 59.67 years and median to be 58yrs. 59 were males and 31 were females. In all 90 patients, none died because of the complications of TACE. 3 out of these 90 patients died within 6 months of procedure, while 11 died within 1 year. So this resulted in 14 patients out of 90 (15%), who could not survive after 1 year of TACE. 76 patients remained alive with survival rate of 84.4%.

Conclusion: TACE is an effective treatment option for advanced unresectable HCC. Our study showed that, the overall survival benefit for such patients is tremendously improved if they are managed with TACE.

Key Words: Transarterial chemoembolization, Hepatocellular carcinoma, arterial supply

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer and is associated with more than 600,000 cases diagnosed worldwide each year[1]. About 80% of all cases are found in Asia[2]. The incidence in the United States continues to increase, mainly due to the concomitant increase in hepatitis C virus infections[3]. Other histologic types of primary liver cancer, including intrahepatic cholangiocarcinoma, while less common than HCC, are also experiencing a rise in incidence[4].

In Pakistan, most HCC patients still present with advanced disease and symptoms directly related to the tumor or hepatic decompensation. The etiology of HCC varies worldwide and it is still not known whether HCCs of different etiologies have different prognosis. With the shift in etiology, HCV has replaced HBV as the major cause of HCC in Pakistan[5].

Unfortunately, tumors in most patients are found to be unresectable at the time of presentation, leaving palliative therapy as the only option. This has resulted in increased utilization of inimally invasive strategies as therapeutic options for both primary and metastatic hepatic malignancies[6,7]. These loco regional therapies include ablative techniques and catheter based approaches. Ablation can be applied either chemically (percutaneous ethanol injection) or thermally (radiofrequency ablation, microwave ablation and laser ablation). Catheter-based approaches include Transarterial chemoembolization (TACE) and transarterial radioembolization. During TACE, intra-arterial chemotherapy and arterial embolization are believed to act in a synergistic manner. A key theoretic advantage of TACE over systemic chemotherapy is that the chemotherapeutic agents used are not intravenously infused throughout the systemic circulation; rather, they are administered locally through the hepatic artery[8]. Thus, the subjectively reported side effects of TACE are mild compared with those caused by systemic chemotherapy.

Transarterial chemoembolization (TACE) is the most promising palliative modality for unresectable HCC[9] and those who have good control or shrinkage of the tumor may even become suitable candidates for surgical resection or transplantation[10]. It can also be used in combination with RFA (Radiofrequency Ablation).

Several studies have reported that TACE inhibits tumor angiogenesis and induces tumor cell apoptosis, while others have found that TACE stimulates tumor

angiogenesis and thus increases the proliferative activity of the tumor cells to some degree[11].

So my study will highlight the survival benefits of TACE in patient who are not suitable for surgery, as have unresectable disease at the time of presentation or due to failed systemic chemotherapy resulting in disease progression.

MATERIALS AND METHODS

We retrospectively analyzed prospectively collected data on all patients with HCC who were evaluated at Shaukat Khanum Cancer Hospital for possible TACE between 1st July 2009 to 30th June 2010. For all of these patients, the diagnosis of HCC was based on either the findings in histologic specimens obtained with needle biopsy or the finding of a hypervascular lesion on Biphasic MDCT images in addition to an alpha-fetoprotein level higher than 400 U/L (400 μg/L). Only those patients who were not suitable for curative therapies such as resection, liver transplantation, or percutaneous intervention were considered for TACE. Patients were required to be at least 18 years old, have preserved liver function (Child-Pugh class A) without substantial liver decompensation,. Encephalopathy, severe variceal bleeding, and/or either ascites, marked thrombocytopenia, prolonged impaired renal function, acute renal failure, or severe liver failure was considered an absolute contraindication to TACE. All patients provided written informed consent before undergoing any study-specific procedures. Only those patients whose baseline evaluation was performed at our institution were included. Baseline evaluation included complete blood cell count, a biochemical profile, and dynamic CT imaging.

Chemoembolization Technique: All chemoembolizations were performed by a single experienced interventional radiologist and by using the same technique. An 18-gauge single-wall needle was used with the Seldinger technique to access the right common femoral artery. A 5-F vascular sheath was placed in the right common femoral artery over a 0.035-inch guidewire (Terumo Medical, Somerset, NJ). With fluoroscopic guidance, a 5-F glide Simmons-1 catheter (Cordis, Miami, Fla) was advanced into the aortic arch and then used to select the celiac axis. The catheter was advanced over the guidewire and into the desired hepatic artery branch, depending on the tumor location. Selective catheterization was performed to achieve lobar or segmental embolization based on the targeted lesions. A solution containing 50 mg of doxorubicin (Adriamycin; Pharmacia-Upjohn, Kalamazoo, Mich) in a 1:1 mixture with iodized oil was infused and followed by the infusion of gelatin-coated trisacryl microspheres (Embosphere particles; Biosphere Medical, Rockland, Mass) until stasis was achieved.

Data Collection Procedure: According to the protocol, patients underwent contrast material– enhanced Biphasic CT scan 4–6 weeks after TACE for assessment of tumor response. Complete blood cell counts and biochemistry profiles were acquired to assess toxicity. Patients with nearly complete tumor necrosis were followed up with CT scan, complete blood cell counts and biochemistry profiles every 6–8 weeks. Patients with residual enhancement and a maintained clinical performance status underwent additional TACE treatment(s).

At the time of analysis, the survival statuses of all patients were documented. A decision was also made to exclude from the analysis any measurements that had been obtained within 3 weeks after TACE. This decision was based on the fact that transient transaminase elevation is a normal response to TACE (without clinical consequences) that is seen in nearly all patients who undergo this treatment. Typically, up to three separate TACE treatments are performed in a treatment cycle, similar to systemic chemotherapy cycles. The decision to repeat treatment was based on residual enhancement seen at CT imaging.

We chose two time points at which to analyze the data: 6 months after the first TACE for evaluation of survival after a complete TACE cycle and 1 year after TACE for assessment of the long-term effect of TACE on survival.

Data Analysis Procedure: The goal of our analysis was to estimate the survival rate at 6-month and 1-year follow-up after the first TACE.

Study variables and information collected on the proforma were entered on the Statistical Package for Social Sciences (SPSS), version 14.0 and analyzed. Age (quantitative variable) was presented as mean +/- standard deviation. Gender was shown as proportion and percentage. Survival rates were measured by Kaplan-Meier Method.

RESULTS

a) **Patient Characteristics:** At analysis of the information in our database, we identified a total of 90 patients. The diagnosis of HCC was confirmed at histologic examination in 59 (66%) patients. The diagnosis of HCC in the remaining 31 patients was based on cross-sectional Biphasic CT imaging findings and elevated serum alpha-fetoprotein levels.

Patients age distribution is shown in Table 1 and 2. There were 59 male and 31 female patients (mean age, 65 years; age range, 18–84 years), shown in Table 3.

28 patients had chronic hepatitis B, and 62 had chronic hepatitis C. All patients had Child-Pugh class A cirrhosis.

61 patients had multiple liver tumors.

The average number of TACE sessions performed per patient was 2.4 (range, 1–3).

b) **Survival:** The data of all patients were included in the survival analysis. 3 patients out of 90(3.3%) died at 6 months and 11(12.22%) died at 1 year.

Cumulative survival rates were 96.66% at 6 months and 84.4% at 1 year [Fig. 1, 2]

Table No.1: Descriptive statistics of age of patients under study

Age of Patient (Years)	**N**	90
	Mean	59.67
	Standard Deviation	9.49
	Minimum	34
	Maximum	84
	Range	50

Table No.2: Age distribution of the subjects under study

Age (Year)	Number	Percentage
34-50	15	16%
51-60	38	42%
61-70	24	26%
71-80	12	13%
≥ 80	1	1.1%
Mean ± SD	**59.67 ± 9.49 years**	

Table No.3: Gender distribution of the subjects under study

		Frequency	Percent
Gender of Patient	**Male**	59	65.5%
	Female	31	34.4%
	Total	90	100.0%

Table No.4: Case Processing Summary

		Censored	
Total N	**N of Events**	**N**	**Percent**
90	14	76	84.4%

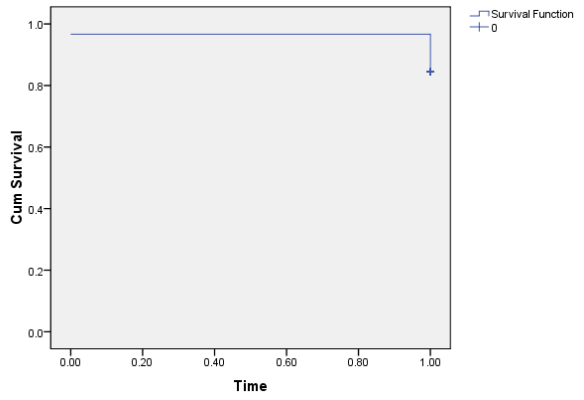

Figure No.1: Survival Function

DISCUSSION

HCC is one of the most common fatal cancers in the world. The prognosis is invariably poor, with a mean survival time of 6 months[12]. Unfortunately, only a selected percentage of patients (10%–15%) are candidates for curative therapies because of the advanced stage of their disease at the time of diagnosis or the presence of comorbidity[13]. TACE has become the mainstay of treatment for patients with nonresectable HCC.

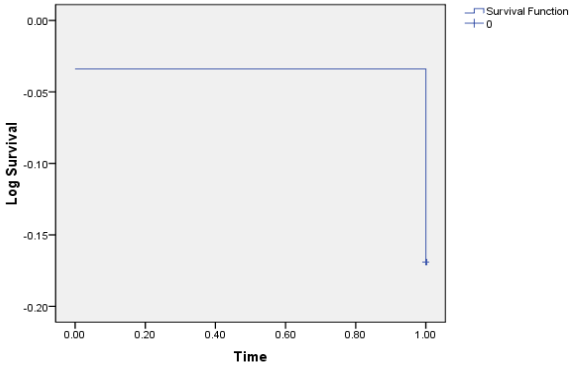

Figure No.2: Log Survival Function

The results of several nonrandomized trials have demonstrated the positive effect of TACE in terms of increased tumor necrosis, as well as the improvements in patient survivals[14]. However, few controlled randomized studies have been published. Early randomized clinical trials revealed no survival benefit for patients with HCC who were treated with TACE [15]. This can be explained by the fact that in these early trials, either the enrolled patients or the methods used for TACE were heterogeneous. HCC is especially difficult to treat with systemic chemotherapy, and although multiple clinical trials have been performed to many single and combined-agent chemotherapies, to our knowledge, no regimen has facilitated a substantial tumor response or survival benefit. Furthermore, systemic toxicity is a well known disadvantage of chemotherapy. Sorafenib, an oral multikinase inhibitor, has induced partial tumor response; however, clinical trials are still underway and an extensive toxicity profile has yet to be determined[16]. We believe that locoregional therapy, such as TACE, is unique because it delivers highly concentrated doses of chemotherapy to the tumor in a specific manner while preserving the nontumorous healthy liver tissue. In theory, this should prevent the occurrence of major systemic side effects.

Numerous studies have shown that chemoembolization causes substantial tumor necrosis (60% to 100%), especially when intra-arterial chemotherapy is followed by particle embolization. However, accurate prediction of the degree and consistency of necrosis achieved after chemoembolization has proven difficult. Since many tumors may be targeted selectively, tumor necrosis does not appear to harm functional liver tissue, as demonstrated by a recent study that found no worsening of liver function following TACE in patients with Child's class A or B liver disease[17].

Reported survival rates after TACE in patients with HCC vary between 60% and 88% at 1 year, between 30% and 60% at 2 years, and between 18% and 50% at 3 years, depending on several risk factors, such as Child-Pugh class, alpha-fetoprotein level, and presence or absence of portal vein thrombosis[19]. In the present study, survival rates were 96.6% at 6 months and 84.4% at one year; however, we did not stratify the patients for potential risk factors. The relative risk factors for Child-Pugh class B cirrhosis (compared with Child-Pugh class

A disease) and portal vein thrombosis are reported to be 1.72 and 1.58, respectively, and therefore may influence survival rates[20].

In the present study, we used a combination of cisplatin (100 mg), doxorubicin (50 mg), and lipiodol (10-20 ml), followed by particulate embolization using gelatin sponge. The procedure was performed by cannulating the feeding artery superselectively (going as close to the tumor as possible using microcatheters), thus minimizing the risk of non-target embolization. This method of super selective cannulation has been identified as a favorable prognostic factor for the disease-free survival of patients following TACE[21].

These data clearly support the role of TACE in the treatment of patients with nonresectable HCC. Our results give clinicians a good overview of the survival benefits of TACE and thereby will be helpful for optimizing treatment strategies.

CONCLUSION

In conclusion, HCCA is a leading cause of death worldwide. TACE is an effective treatment option for advanced unresectable HCC. TACE can achieve better initial local tumor control and longer time to disease progression for unresectable HCC. Our study showed that, the overall survival benefit for such patients is tremendously improved if they are managed with TACE.

Despite a series of randomized trials that have not shown increased survival, recent RCTs convincingly demonstrate that chemoembolization improves patient survival. Chemoembolization has become the mainstay of treatment for patients with unresectable HCC. While TACE is not a cure for HCC, it is an effective therapy that merits further study.

REFERENCES

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005; 55:74-108.
2. Lai EC, Lau WY. Abstract of: The continuing challenge of hepatic cancer in Asia. Surgeon. 2005[cited 2005 Jun]; 3(3):210-5. Available from: http://www.biowizard.com/
3. El-Serag HB, Mason AC. Rising incidence of Hepatocellular carcinoma in the United States. N Engl J Med 1999; 340: 745-50.
4. DeOliveira ML, Cunningham SC, Cameron JL, Kamangar F, Winter JM, Lillemoe KD, et al. Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. Ann Surg 2007;245: 755-62.
5. Khokhar N, Aijazi I, Gill ML. Spectrum of Hepatocellular carcinoma at Shifa International Hospital, Islamabad. J Ayub Med Coll Abottabad 2003; 51: 64- 70.
6. Dodd GD, III, Soulen MC, Kane RA, Livraghi T , Lees WR, et al. Minimally invasive treatment of malignant hepatic tumors: at the threshold of a major breakthrough. Radiographics 2000; 20:9-27.
7. Goldberg SN, Ahmed M. Minimally invasive image-guided therapies for hepatocellular carcinoma. J Clin Gastroenterol 2002; 35(5Suppl 2):S115-29.
8. Cagol PP, Pasqual E, Bacchetti S. Potential advantages of locoregional intra-arterial chemotherapy. In Vivo 2006;20:777-9.
9. Lau WY, Lai EC. Hepatocellular carcinoma: current management and recent advances. Hepatobiliary Pancreat Dis Int[abstract]. 2008 [cited 2008 Jun];7(3):237-57. Available from: BioWizard, Inc.
10. Treatment of Liver Cancer: Hepatitis B Foundation [online] [cited]. Available from:URL: http://www. hepb.org/index.html
11. Wang B, Xu H, Gao ZQ, Ning HF, Sun YQ, Cao GW. Increased expression of vascular endothelial growth factor in hepatocellular carcinoma after transcatheter arterial chemoembolization. Acta Radiol [abstract]. 2008[cited 2008 Jun]; 49(5): 523-9. Available from: http://www.biowizard.com/
12. Capocaccia R, Sant M, Berrino F, Simonetti A, Santi V, Trevisani F. Hepatocellular carcinoma: trends of incidence and survival in Europe and the United States at the end of the 20th century. Am J Gastroenterol 2007;102:1661–1670.
13. Stuart KE, Anand AJ, Jenkins RL. Hepatocellular carcinoma in the United States: prognostic features, treatment outcome, and survival. Cancer 1996; 77:2217–2222.
14. Barone M, Ettorre GC, Ladisa R. Transcatheter arterial chemoembolization (TACE) in treatment of hepatocellular carcinoma. Hepatogastroenterol 2003;50:183–187.
15. Pelletier G, Roche A, Ink O. A randomized trial of hepatic arterial chemoembolization in patients with unresectable hepatocellular carcinoma. J Hepatol 1990;11:181–184.
16. Abou-Alfa GK, Schwartz L, Ricci S. Phase II study of sorafenib in patients with advanced hepatocellular carcinoma. J Clin Oncol 2006;24: 4293–4300.
17. Caturelli E, Siena DA, Fusilli S. Transcatheter arterial chemoembolization for hepatocellular carcinoma in patients with cirrhosis: Evaluation of damage to nontumorous liver tissue—long-term prospective study. Radiology 2000;215:123-128.
18. Lai CL, Wu PC, Chan GC, Lok AS, Lin HJ. Doxorubicin versus no antitumor therapy in inoperable hepatocellular carcinoma: a prospective randomized trial. Cancer 1988;62:479–483.
19. Geschwind JF, Ramsey DE, Choti MA, Thuluvath PJ, Huncharek MS. Chemoembolization of hepatocellular carcinoma: results of a metaanalysis. Am J Clin Oncol 2003;26:344–349.
20. A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients: the Cancer of the Liver Italian Program (CLIP) investigators. Hepatology 1998;28:751–755.
21. Ji SK, Cho YK, Ahn YS, Kim MY, Park YO, Kim JK, et al. Multivariate analysis of the predictors of survival for patients with hepatocellular carcinoma undergoing transarterial chemoembolization: Focusing on superselective chemoembolization. Korean J Radiol 2008;9:534-40.