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The Outcome of Large (> 5cm) Hepatocellular Carcinoma in Patients with Alcoholic and Cryptogenic Cirrhosis, Treated with Transarterial Chemoembolization. A Tertiary Care Centre Experience

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Keywords:

Hepatocellular carcinoma; Cirrhosis; Transarterial chemoembolization

1. Abstract

1.1. Introduction: This retrospective study investigated the outcome of large unresectable Hepatocellular Carcinoma (HCC) in patients with alcoholic and cryptogenic cirrhosis, treated with Trans-Arterial Chemoembolization (TACE). **1.2. Methods:** Consecutive 43 cirrhotic patients [Alcoholic group – 25, (M: 25, mean age 62±9.7 SD years, Cryptogenic group – 18, (M: 16, mean age 65±5.6 SD years) with unresectable HCC underwent single /or multiple course of TACE during 01.01.2018 to 31.01.2021.

1.3. Results: Two groups were matched in age and BMI. The alcoholic cirrhosis group the mean survival was 12.1±3.6 SD months whereas the cryptogenic group had a mean survival of 15.3±6.2SD months, (mean survival of Alcoholic HCC group Vs Cryptogenic HCC group, P = 0.04). The over role survival beyond 12 months is about 20% and the life expectancy beyond 18 months was not seen in any of the patients, irrespective of the number of times of TACE or the aetiology of the underlying cirrhosis. However single tumours, low AFP levels and low PST scores showed relatively a better survival. Fourteen patients had post-embolization syndrome, 3 developed liver failure, 01 had an acute cardiac failure whereas majority (58.1%) were free of significant complications.

1.4. Conclusions: TACE is considered to be a therapeutic option for large HCC. However, the prognosis with patients who were associated with alcoholic cirrhosis seems to be poor.

2. Introduction

Hepatocellular Carcinoma (HCC) is the fifth most common solid tumour in the world, and the third most common cause of cancer death [1, 2]. Hepatitis B, hepatitis C and alcoholic cirrhosis are the commonest aetiological factors for HCC in the world [3-7]. However, the reported prevalence of hepatitis B and C is low in the country [8, 9]. Most of the Sri Lankan patients with HCC have been diagnosed of having either alcoholic cirrhosis or cryptogenic cirrhosis.

Regular screening programmes to detect HCC for high risk patients are not well established in Sri Lanka. Therefore, large tumours with decompensated cirrhosis are a common late presentation. Although surgical resection is curative, an occasional patient is suitable for surgery due to poor liver functions and portal hypertension. Transarterial chemoembolization (TACE) is the only palliative treatment option available for these patients with large hepatomas in Sri Lanka at present. The aim of this retrospective study was to assess the outcome of large unresectable Hepatocellular Carcinoma (HCC) in patients with alcoholic and cryptogenic cirrhosis, treated with trans-arterial chemoembolization (TACE).

3. Methods

Out of 64 consecutive patients with HCC, 43 cirrhotic patients with HCC were enrolled in this study. These patients were referred to gastroenterology unit of the National hospital of Sri Lanka from 01.01.2018 to 31.01.2021. Twenty-one of them excluded from the study, according to exclusion criteria. Diagnosis of alcoholic or cryptogenic cirrhosis was established through medical history, physical examination, abdominal ultra-sound scan, liver disease screening profile and liver function tests. Diagnosis of HCC was made on radiological findings, alpha-fetoprotein level and cytology or histology according to the Barcelona criteria [10]. Unresectable HCC was defined as not treatable by surgical resection due to presence of portal hypertension with or without elevated serum bilirubin. Liver transplantation is not available in Sri Lanka and it could not be afforded in a foreign country for this cohort of patients. The performance status of the patients was assessed according to the performance status test (PST) for cancer patients [11, 12]. The extra-hepatic spread of HCC was assessed by contrast CT and MRI accordingly. Patients with unresectable HCC of Childs grade B cirrhosis due to alcoholic or cryptogenic in origin were included to the study whilst patients with portal vein thrombosis, extra-hepatic tumour spread, Childs grade A and C cirrhosis and >1.5mg /dl of serum creatinine were excluded from the study.

TACE was carried out through selective hepatic arterial catheterization. Tumour was super selectively catheterised when possible, using microcatheter (0.018 -2F, Mira Flex TM, Cook medical, USA) and a mixture of 30 -50 mg of Doxorubicin (Rapid dissolution, powder for injection, Pharmacia limited, Kent) and 5-10 ml of lipiodol (Laboratoire Guerbet, Paris, France). The feeding arteries were then embolized with 2-3 mm strips of gelfoam (Upjohn Co, Kalamazoo, MI, USA). The TACE was attempted all the time by targeting all the tumours in the presences of multiple tumours and subsequent attempts were made in techniquely demanding situations. (range of number of settings: 2-6, range of interval between setting: 2-4 weeks).

Adverse reactions after TACE were recorded. Post-embolization syndrome was defined as fever, abdominal pain or vomiting during first 3 days following TACE. Liver failure after TACE was defined as the occurrence of hepatic encephalopathy, ascites or elevation of serum bilirubin. All patients were followed up regularly and assessed for tumour response by AFP level and computerized scans every 10 -12 weeks after TACE. Subsequent TACE was carried out if tumour response was poor (tumour shrinkage in contrast CT < 0.5-1 cm) or recurrence of the tumour. Overall survival was calculated from the date of HCC was diagnosed to the time of death. All patients who were given TACE were followed until their death. Ethical clearance was obtained from the National Hospital of Sri Lanka.

4. Statistical Analysis

Data are expressed as mean +/- SD and analyzed using a Statistical Package for Social Sciences version 11, (SPSS 11.0, Chicago, Illinois, USA). The mean of the relevant variables of the patients were compared using the t-test. Significance was assigned to a p-value of <0.05.

5. Results

There were 25 alcoholic cirrhosis and 18 cryptogenic cirrhosis patients in this cohort and their mean ages, body mass indexes (BMI), tumour sizes, Alfa fetoprotein levels, and staging scores were similar (Table 1). Although these patients were Childs group B, their PST scores were different. Therefore, majority of patients were BCLC stage B and rest of them fulfilled BCLC stage C criteria simply because their PST scores were higher. Median follow up of the patients was 18 months. Among the alcoholic cirrhosis group, the mean survival was 12.1±3.6SD months whereas the others, had a mean survival of 15.3±6.2SD months, (mean survival of Alcoholic HCC group Vs Cryptogenic HCC group, P = 0.04).

The survival beyond 12 months is about 20% of the patients, whereas the life expectancy beyond 18 months was not seen in any of the patients, irrespective of the number of times the TACE was given or the aetiology of the underlying cirrhosis (Alcoholic or Cryptogenic cirrhosis). However single tumours, low AFP levels and low PST scores showed relatively better survival (Table 2). Adverse reactions of TACE were seen among our patients (Table 3), 14 patients experienced post-embolization syndrome, 3 patients developed liver failure, 01 patient had acute cardiac failure whereas majority (58.1%) were free of significant complications.

Table 1: Patients' characteristics

	Alcoholic cirrhosis (n= 25)	Cryptogenic cirrhosis (n= 18)	P value
Age (mean ± SD)	62±9.7	65±5.6	0.1
Sex M:F	25:0	16:2	
BMI (mean ± SD)	20±1.8	19±2.1	0.2
AFP level (%)			
< 400ng/ml	66	62	
>400ng/ml	34	38	
Tumour size (cm)			
Mean± SD	6.5±1.1	6.6±1.2	0.1
range	4.5 - 9	4.6 - 9.5	
Multifocal tumours (%)	24	27	
Child Pugh score mean ± SD	8±0.52	8±0.43	0.1
Performance status test (%) 0 1 2	 60 24 16	 56 28 16	

Table 2: Mean survival comparison of different tumour characteristics

	Number	Mean survival months	P
Single tumours	28	16.1±2.3 SD	0.03
Multifocal tumours	15	11.1±2.6 SD	
AFP			0.02
<400	23	17.2±2.1SD	
>400	20	14.4±1.6SD	
PST			0.01
0	29	16.2±2.SD	
1	12	11.4±2.8SD	
2	7	9.4±3.2SD	

Table 3: Complications of TACE

Complication	Number (%) of patients with each complication
Post-embolization Syndrome	32.5 (14/43)
Liver failure	6.9 (3/43)
Cardiac failure	2.3 (1/43)
No significant adverse reactions	58.1 (25/43)

6. Discussion

In many countries, TACE is considered the standard treatment for unresectable HCC on the basis of the fact that there is no alternatives [11-13]. Meta-Analysis of data from five trials has shown that in comparison with non-active treatment, TACE significantly decreases the overall 2-year mortality [12 -18]. Overall survival rate in our patients are poor compared to published studies [16-18]. However, patients with underlying cryptogenic cirrhosis had slightly a better outcome compared to alcoholic cirrhotic group (15.3±6.2 SD / 12.1±3.6 SD months / p = 0.04). The survival beyond 12 months was about 20% of the patients. The life expectancy beyond 18 months was not reported among any of the patients, irrespective of the number times the TACE was given or the group that the patients were belong to (Alcoholic or Cryptogenic cirrhosis).

The reason for poor survival is multifactorial. Firstly, this cohort includes large tumours including single as well as multifocal up to 4 tumours compared to most of the published studies. Secondly, different aetiology of liver cirrhosis in this cohort of patients or the staging system which was used to categorized the tumours. The sample size is also not great to achieve good results but numbers are comparable to other series. Sub analysis showed that means survival rate is better in single tumours compared to multifocal (16.1±2.3SD vs 11.1±2.6SD) irrespective of their aetiology. A large variability in the chemoembolization protocol and strict patient selection criteria among the published trials has to be considered when comparing the outcome [13-14].

The causes of cirrhosis and HCC in most of the published studies are viral in origin in particularly southeast Asia and that could be one of the reason for better survival rates [3, 5-7]. However, a study has shown that intra-arterial chemotherapy is more effective for HCC induced by alcohol compared to hepatitis B15. But, only 9 patients with alcoholic cirrhosis with HCC were included in that study. Another study from France has shown that cryptogenic cirrhosis has bad prognosis compared to hepatitis C induced cirrhosis16-18. In keeping with published studies even in this cohort, higher AFP levels had a poor outcome.

All our patients belong to Child grade B cirrhosis, they had no extrahepatic metastasis, non-thrombosed portal veins but their PST score was different. Therefore, their BCLC stage is either B or C simply due to their PST score. BCLC stage B (PST -0) patients had better survival compared to BCLC stage C (PST >1) as expected. This study shows that multifocal tumours, higher AFP level, Higher BCLC stage and higher PST scores were poor prognostic indicators. Therefore, all these factors need to be considered as selection criteria for TACE procedure.

TACE is a relatively safe procedure with a modest risk of minor complications such as post-embolization syndrome (Table 3). There were 3 patients with post TACE liver failure and 1with cardiac failure. There were no other major post TACE complications such as gastrointestinal bleeding, cholecystitis or liver abscesses as reported by other studies [16-18].

7. Conclusion

Survival rates of unresectable HCC due to alcoholic or cryptogenic cirrhosis, undergoing TACE was not very satisfactory. Patients with cryptogenic cirrhosis had slightly better survival than alcoholic cirrhotic group.

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