Original Article

Analysis of the Outcomes of Transarterial Chemoembolization as A Bridge Therapy to Liver Transplant for Hepatocellular Carcinomas: A Single-Centered Retrospective Study

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ABSTRACT

Objective: To determine the outcomes of transarterial chemoembolization (TACE) as a bridging therapy to liver transplant for Barcelona clinic liver cancer (BCLC) stage A hepatocellular carcinoma.

Methodology: This retrospective study comprised data of 40 patients with BCLC stage A hepatocellular carcinoma (HCC) who received TACE as a bridge therapy prior to liver transplant from January 2022 to June 2022. Tumor response to TACE was assessed on imaging based on modified response evaluation criteria in solid tumors (mRECIST). All the descriptive statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 25.

Results: In this study, the mean age of included patients was 56.68±7.17 years. The mean pre-TACE tumor size was calculated as 3.56±10.69 cm. Post-TACE imaging response showed complete response in 13 patients, partial response in 11 patients, and progressive disease in 7 patients. Of the 40 patients, 4(10%) patients were dropouts from waiting list, 6(15%) individuals underwent liver transplant (LT) after bridging TACE, 1 (2.5%) patient opted for hepatic wedge resection for HCC instead of LT, and 7(17.5%) patients were lost to follow-up. Twenty two (55%) patients were still in waiting list (mean waiting time=273±30 days) for LT.

Conclusion: Transarterial chemoembolization as a bridge therapy prior to LT for early stage HCC has beneficial results and reduces dropout rates during waiting time.

Keywords: *Liver transplant. Hepatocellular carcinoma. Transarterial chemoembolization.*

INTRODUCTION

Hepatocellular carcinoma is the worldwide fastest growing cause of cancer-related deaths, with patients having a 5 year survival rate of less than 12%.[1] Globally, HCC is the fifth most common cancer and second most common cause of cancer-related deaths.[2] Liver transplant has emerged as the preferred treatment option for early-stage HCC patients with advanced liver disease. Through the removal of the cirrhotic liver, the primary risk factor for HCC, liver transplantation provides a chance to both treat and prevent de novo HCC.[3] The accepted standard indication for LT is HCC which meets the Milan criteria introduced in 1996.[4] Milan criteria include patients with one tumor of <5 cm diameter or up to three tumor foci, each having a diameter of <3 cm with no vascular invasion and no extrahepatic metastasis.[4] These individuals have a 70% five year survival rate and a recurrence rate of less than 20%.[5]

However, due to the scarcity of liver donors, not all HCC patients can receive transplantation immediately, which results in a long waiting list and subsequently a high dropout rate of 30-40% per year due to tumor progression.[6] If HCC is left untreated, dropout rates at 6 months and 1 year are estimated to be as high as 12% and 15-30%, respectively.[5] In order to lower the dropout rate, most centers have adopted the practice of treating HCC patients with locoregional therapies as a bridge to slow tumor growth prior to LT while they await transplantation if the anticipated waiting period is more than six months.[7] In patients with HCC within Milan criteria, bridging therapy is estimated to decrease the dropout rate to 0-10%.[5] The main bridging treatment options for HCC patients prior to LT include transarterial chemoembolization, radiofrequency ablation, liver resection, and stereotactic body radiation therapy (SBRT).[8] Among all the candidates with end-stage liver disease, HCC patients have the highest rates of waiting time for LT.[7] Transarterial chemoembolization and radioembolization are the two main intraarterial techniques used in the treatment of HCC. So far, no recommendation can be made for preferring one type of intraarterial locoregional treatment over another prior to LT.[7]

For patients who do not initially meet the criteria for LT, another goal of locoregional therapy is to reduce the tumor load until it is within the acceptable criteria, allowing them to be added to the waiting list for LT.[9]

This retrospective study aimed to analyze the outcomes of TACE as a bridging therapy to liver transplant for early-stage Barcelona clinic liver cancer hepatocellular carcinomas.

METHODOLOGY

This cross-sectional study was conducted at the

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Radiology Department of Pakistan Kidney and Liver Institute and Research Centre, Lahore. This study was approved by the institutional review board of the institute. All the TACE procedures were performed after informed written consent by a consultant interventional radiologist with more than five years of experience in the field. This study comprised data of 40 consecutive patients with HCC who received TACE as a bridge therapy prior to liver transplant from January 2022 to June 2022. All the patients were followed-up for at least four months after the last bridging TACE received by the patient.

Inclusion criteria were all adults with early stage BCLC HCC within Milan criteria. Patients with angioinvasion, extrahepatic disease, and Eastern Cooperative Oncology Group performance status >2 were excluded from the study. Only patients with HCC whose anticipated waiting time for LT was longer than three months were considered for bridging TACE.

Prior to TACE, each patient had a triphasic computed tomography (CT) examination including the arterial, portal-venous, and delayed phases using multidetector scanners as part of the preoperative work-up. The prerequisites for TACE were an appropriate blood clotting profile with a partial thromboplastin time <38 seconds, an international normalized ratio <1.5, and a platelet count of $150\text{-}400x10^9$/L.

After obtaining written informed consent from all the patients, super-selective TACE was performed under fluoroscopic guidance by injecting chemotherapy emulsion (50 mg doxorubicin-10 mL Lipiodol emulsion) to chemo-embolize the tumor followed by postprocedure embolization of the feeding vessel with polyvinyl alcohol particles to obtain adequate stasis in the tumor-feeding vessels.

All post-TACE patients were followed after 6 weeks with triphasic CT abdomen or dynamic contrast-enhanced magnetic resonance imaging (MRI) liver and then discussed in the liver transplant multidisciplinary meeting. Tumor response to TACE was assessed on imaging based on modified response evaluation criteria in solid tumors. According to mRECIST criteria, complete response was defined as the disappearance of arterially enhanced areas in the targeted lesion; partial response (PR) was defined as at least a 30% reduction in the sum of viable tumor diameter taking the baseline sum of the target lesions diameter as a reference; progressive disease (PD) was defined as at least a 20% increase in the sum of the longest diameter of viable tumor; and stable disease was defined as any case that is ineligible for PD or PR.[10] For patients with residual or recurrent tumors, re-TACE treatment was done after re-assessment in multidisciplinary team meetings. Patients who had tumor progression beyond Milan criteria after TACE were dropped out, whereas those who had minimal progression (progression that did not meet the mRECIST criteria), stable disease or tumor regression proceeded for LT.

STATISTICAL ANALYSIS

Data was recorded on an Excel sheet and subsequently exported to the Statistical Package for the Social Sciences (SPSS) version 25 for statistical analysis. Numerical variables were measured as mean and standard deviations, whereas categorical variables were expressed as frequencies and percentages.

RESULTS

In this study, 40 patients selected for bridging therapy prior to LT had a mean age of 56.68±7.17 years. Among them, 30(75%) were males and 10(25%) were females. All patients received TACE as a bridge therapy. The etiologies of end stage liver disease were hepatitis C virus (HCV) infection in 33(82.5%) patients, hepatitis B virus (HBV) infection in 1(2.5%) patient, HBV and HCV co-infection in 3(7.5%) patients, and non-alcoholic fatty liver disease (NAFLD) in 1(2.5%) patient (Table 1).

Based on mRECIST criteria, post-TACE imaging response was evaluated after six weeks which showed complete response in 13 patients, partial response in 11 patients, and progressive disease in 7 patients (Figure 1).

All patients had early-stage HCC (BCLC stage A), according to the BCLC staging. The mean pre-TACE tumor size was 3.56±10.69 cm. Among 40 patients, 28(70%) patients had solitary HCC nodule, 8(20%) patients had two HCC nodules, and 4(10%) patients had three HCC nodules. All patients fulfilled the Milan criteria prior to the bridging TACE therapy. Child-Pugh A cirrhosis was observed in 31(77.5%) patients and Child-Pugh B cirrhosis in 9(22.5%) patients. Of 40 patients, 29(72.50%) patients received TACE as bridging therapy once, 8(20%) patients received twice, and 3(7.50%) patients received thrice. Mean pre-TACE alpha-fetoprotein (AFP) was 147.85±308.38 ng/mL and it decreased to 83.56±274.36 ng/mL at 6 weeks follow-up. Aspartate aminotransferase (AST) and alanine transaminase (ALT) were also recorded before TACE (pre-TACE) and one day after TACE (post-TACE) as shown in Table 2.

In this study, 7(17.50%) patients were lost to follow-up. Among the remaining 33 patients, 4(10%) patients had tumor progression beyond Milan criteria despite bridging therapy and were dropped out of the waiting list, 6(15%) patients underwent LT after bridging TACE (mean time=126±56.17 days on the waiting list before LT), and 1(2.50%) patient opted for hepatic wedge resection for HCC (mean time=77 days) instead of LT as his liver was non-cirrhotic. The remaining 22(55%) patients were still in waiting list for LT (mean waiting time=273±30 days) without any evidence of

tumor progression. Of these 22 patients, 10 individuals had complete tumor response to TACE as assessed on CT/MRI imaging, 9 individuals had a partial response, and 3 individuals had progressive disease according to mRECIST criteria but within the Milan criteria. In the transplantation group (n=6), 2 patients had shortened interval to LT post-TACE, so post-TACE imaging could not be done to see tumor response to TACE. In the remaining 4 patients, 3(7.5%) patients had a complete response and 1(2.5%) had a partial response to TACE as assessed on imaging. While in the explanted liver specimen, complete necrosis was reported in 3(7.5%) patients and partial necrosis in the remaining 3(7.5%) patients on histopathological examination. One (2.5%) patient with complete imaging response to TACE had a viable tumor in its explant.

Figures 2 and 3 show complete and partial post-TACE response in the patients having solitary HCC in segment VII.

Table 1: Demographics of the Patients Included in the Study

Characteristic		Frequency & Percentage
Age (Years)	**Mean±SD**	56.68±7.17
Gender	**Male**	30(75%)
	Female	10(25%)
Aetiology of Liver Disease	**HCV**	33(82.5%)
	HBV/HCV Co-Infection	3(7.5%)
	HBV	1(2.5%)
	NAFLD	1(2.5%)
	Cryptogenic	2(5%)
Child-Pugh Cirrhosis	**A**	31(77.5%)
	B	9(22.5%)

Table 2: Study Variables of the Participants

Study Variables		Frequency & Percentage
Number of HCC Nodules	**Solitary**	28(70%)
	Two	8(20%)
	Three	4(10%)
Frequency of TACE as a Bridging Therapy	**Once**	29(72.5%)
	Twice	8(20%)
	Thrice	3(7.5%)
Mean Pre-TACE Tumor Size (cm)		3.56±10.69
Lobar Involvement	**Unilobar**	40(100%)
	Bilobar	0(0%)
Mean Pre-TACE AFP[a] (ng/mL)		147.85±308.38
Mean Post-TACE AFP[b] (ng/mL)		83.56±274.36
Mean Pre-TACE AST[a] (IU/L)		62.13±49.32
Mean Post-TACE AST[a] (IU/L)		115.55±101.87
Mean Pre-TACE ALT[a] (IU/L)		44.52±30.37
Mean Post-TACE ALT[a] (IU/L)		74.48±58.43

[a]of 31 patients
[b]of 25 patients

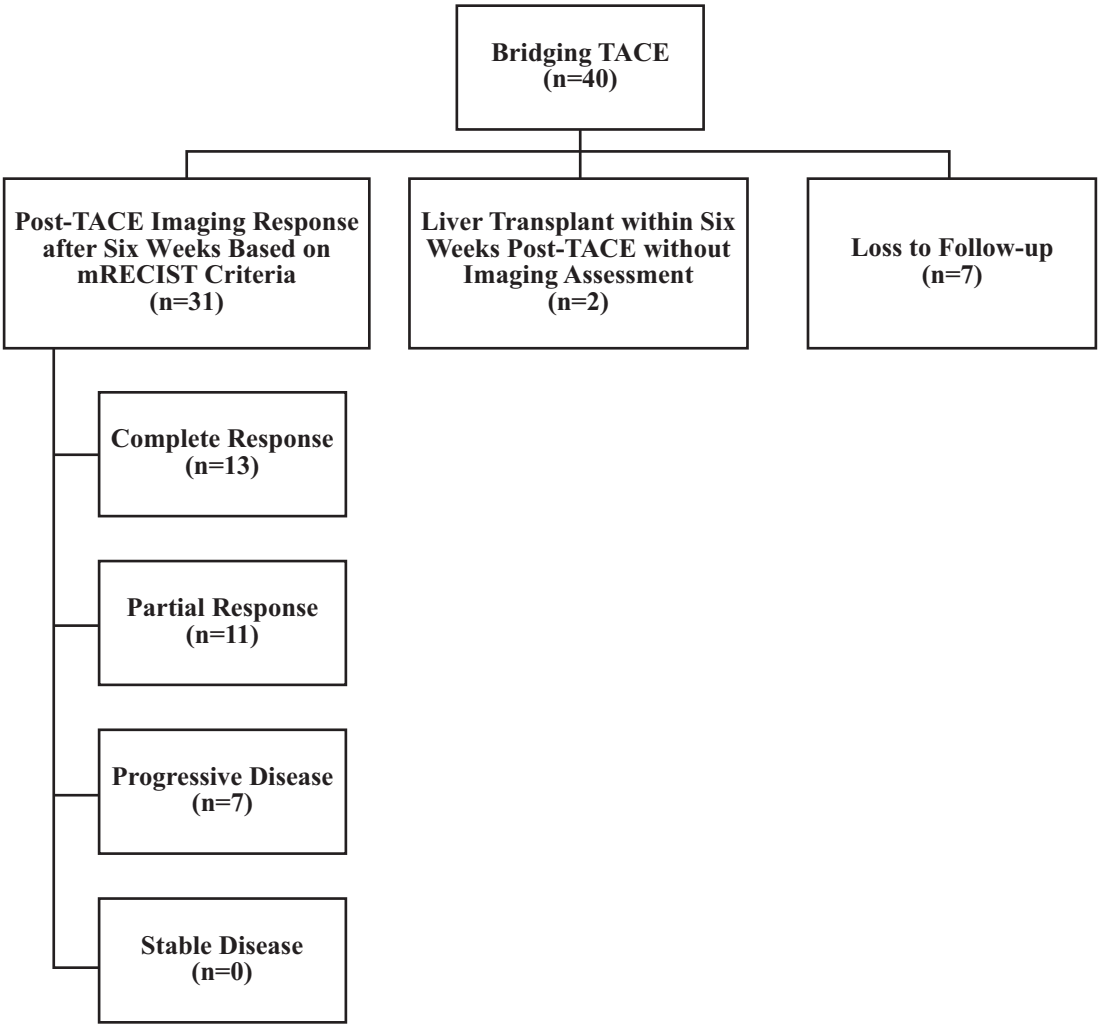
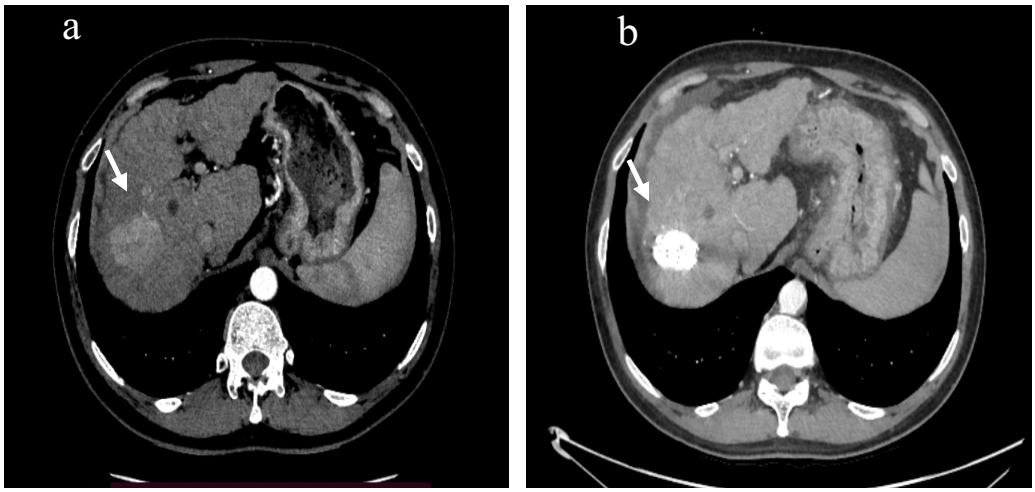


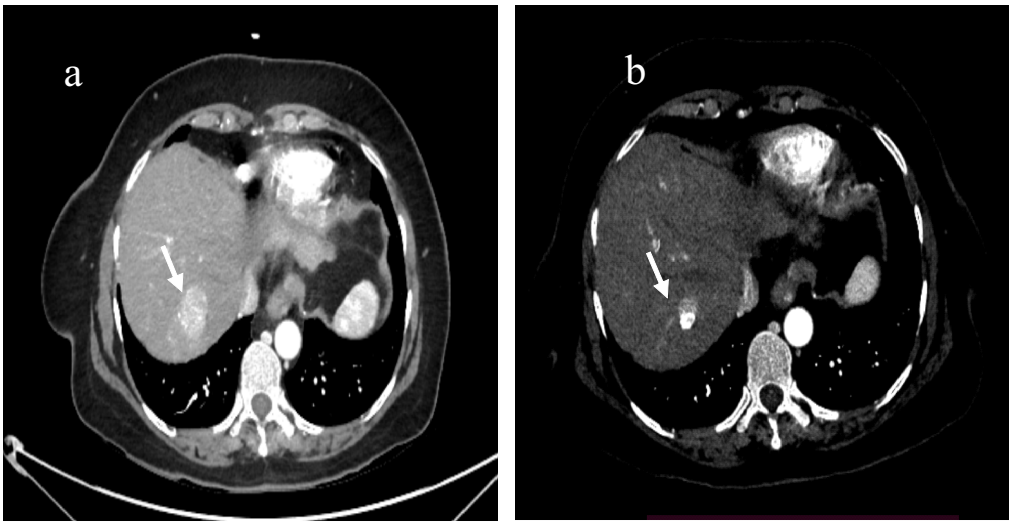
Figure 1: Post-TACE Imaging Response of the Study Participants



(a) Axial contrast-enhanced CT image of the abdomen at the level of the liver in the arterial phase shows an arterially enhancing focal lesion in keeping with HCC in segment VII (white arrow) on a background of the cirrhotic liver.

(b) Axial contrast-enhanced CT image of the abdomen at the level of liver performed 6 weeks after TACE showed the treated lesion is lipiodol packed (white arrow) without any residual disease suggesting complete response.

Figure 2: Complete Post-TACE Response in a 50 Year Old Man with a Solitary HCC



(a) Axial contrast-enhanced CT image of the abdomen at the level of the liver in the keeping with HCC in segment VII.

(b) Axial contrast-enhanced CT image of the abdomen at the level of liver performed 6 weeks after TACE showed the treated lesion is lipiodol packed posteriorly with a residual arterialized component anteriorly (white arrow) suggesting partial response.

Figure 3: Partial Post-TACE Treatment Response in a 55 Year Old Female with a Solitary HCC

DISCUSSION

Liver transplantation has become a widely acknowledged treatment option for patients with HCC who meet the Milan criteria or the University of California, San Francisco criteria.[11] Only transplantation offers a cure for both HCC and the underlying liver cirrhosis.[3] Studies have shown that it is particularly effective in treating early-stage (BCLC stage A) HCCs.[3] As the availability of liver donors (both deceased and living) is limited, not all patients diagnosed with HCC can receive LT immediately. This ultimately leads to a long waiting list and subsequently a high dropout rate of more than 30% per year due to tumor progression beyond the acceptance criteria.[6]

While on the waiting list, the use of locoregional therapies has emerged as a temporary measure to slow tumor progression before transplant. Given the unpredictable waiting time for a liver transplant, nearly all waitlisted HCC patients are treated with locoregional bridging therapy in clinical practice.[12] Many locoregional therapy options are available but currently, there is no guideline for favoring any specific locoregional therapy.[13] Transarterial chemoembolization is the most frequently used intra-arterial bridging therapy globally.[8]

In literature, variable outcomes and dropout rates following bridging treatment have been described but due to the heterogeneity of patient cohorts and wide range of bridging therapy options, it is challenging to determine the exact contribution of bridging therapy to the reduction of dropout rates. In a study, the dropout rate was 8.7% in HCC patients receiving direct-acting antiviral therapy.[14] It is comparable to our study with a 10% dropout rate in HCC patients receiving bridging TACE. It has been shown that the dropout rate decreases when TACE is performed as a bridging therapy prior to LT.[15] Transarterial chemoembolization pretreatment was associated with improved posttransplant survival, with patients experiencing a 44% reduction in posttransplant mortality.[16]

Another study showed that in HCC patients with a high risk of dropping out from waiting list for LT, bridging therapy combining SBRT and TACE may be more beneficial than TACE alone.[1] In 2018, Tan et al. observed that there was no difference between the bridging therapy (BT) group and the non-bridging therapy group in terms of the frequency of waiting list dropouts, although there was a tendency for the waiting duration to be longer in the BT group. As a result, it was concluded that BT might allow the LT candidate with HCC to wait longer.[17]

Till date, there is debate over performing locoregional therapies as a bridge for patients awaiting LT. The reported outcomes of bridging TACE are controversial and its efficacy in lowering dropout rates hasn't been proven by any prospective randomized controlled studies until now. But still, there is general agreement that if the waiting duration is six months or more, locoregional treatment for HCC should be performed to minimize waitlist drop-out.[15]

Imaging (CT/MRI) may also underestimate the presence of persistent or recurrent disease after locoregional therapy.[1] Our results were also consistent with this finding. One of our patients who had a

complete imaging response to TACE still had a viable tumor in its explant on histopathological examination. In this study, 10 out of 22(45.5%) patients showed complete radiological response to TACE. Rubinstein et al. reported similar results showing that 64% of nodules in his study had a complete imaging response to treatment but only 30% had complete tumor necrosis in their explants.[1] Hence, data shows that patients who have had a complete response to treatment on imaging may have a viable tumor in their explants, indicating that better treatment options are required to improve patient outcomes.

In this study, the mean pre-TACE alpha-fetoprotein was 147.85±308.38 ng/mL and it decreased to 83.56±274.36 ng/mL at 6 weeks follow-up. Another study reported that patients with AFP levels of ≥66 ng/mL prior to the LT have poor outcomes after LT independent of Milan criteria. An AFP value of more than 1000 ng/mL was found to be associated with a worse outcome after liver transplantation in HCC that met the Milan criteria.[7]

CONCLUSION

Overall, TACE as a bridge therapy prior to LT for early stage HCCs, has beneficial results and is effective in reducing dropout rates during waiting time. A future extension of this study five years from today may be helpful in determining the survival rate in the transplantation group and the HCC recurrence rate in transplanted livers after bridging TACE.

LIMITATIONS & RECOMMENDATIONS

We acknowledge that our study has few limitations. It was a retrospective and single centered study, hence inherent bias to all such studies could not be excluded. It may carry the risk of bias for the treatment. Our sample size was small and follow-up information was dependent on data available in the hospital record system. Nevertheless, it is the first such study from Pakistan and may provide additional context for prospective studies and randomised controlled trials in comparing different locoregional therapies prior to LT.

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