The Egyptian Journal of Hospital Medicine (July 2018) Vol. 72 (11), Page 5578-5583

Role of Transarterial Chemoembolization (TACE) in Down Staging of Hepatocellular Carcinoma (HCC) before Liver Transplantation

Abdallah Lutfy Farouk Ahmed, Haytham Mohamed Nasser, Mohamed El-Gharieb Abo-Elmaaty, Iman Fawzy Montasser

Radiology Departments, Faculty of Medicine, Ain Shams University

***Corresponding author:** Abdallah Lutfy Farouk Ahmed, **Email:** dr.abdallahlutfy@hotmail.com.

ABSTRACT

Background: liver transplantation (LT) has emerged as the optimal treatment for cirrhotic patients with Hepatocellular carcinoma (HCC) because it cures both tumor and underlying cirrhosis. HCC could be downstaged or controlled by various anticancer therapies, which might bring them chance of undergoing a curative treatment such as LT. **Aim of the Work:** it was to evaluate the outcomes of HCC downstaged patients using transarterial hepatic chemoembolization (TACE) therapy to allow eligibility for liver transplantation. **Patients and Methods:** the study included all the cirrhotic patients who underwent TACE for downstaging of HCC to become eligible for liver transplantation at the period from 2008 to 2017 in Ain Shams Specialized Hospital. Al the patients underwent TACE to meet the Milan criteria for liver transplantation. **Results:** the etiology of cirrhosis and HCC in our patients was primarily Hepatitis C virus which is endemic in our country. All the cases were not eligible for liver transplantation because they were out of Milan criteria, therefore all the cases underwent TACE for downstaging of the tumor to be within the Milan criteria to become fit for liver transplantation. After undergoing TACE for downstaging, Patients underwent living donor liver transplantation, then they were followed up for detection of recurrence on the transplanted liver. Four of the twenty seven patients had recurrent HCC (14.8 %). **Conclusion:** successful down-staging of HCC by TACE can be achieved in the majority of carefully selected patients and is associated with excellent posttransplantation outcome.

Keywords: LT, HCC, TACE.

INTRODUCTION

Hepatitis C virus (HCV) infection is a major public health burden in Egypt, where it bears the highest prevalence rate in the world. Estimates for prevalence are based upon data reported from the 2008 and 2015 Egypt Demographic Health Surveys. Chronic infection with HCV is the leading cause of end-stage liver disease, hepatocellular carcinoma (HCC) and liver-related death in Egypt. HCV causes chronic hepatitis in 60%–80% of the patients, and 10%–20% of those patients develop cirrhosis over 20–30 years of HCV infection. About 1%–5% of the patients with liver cirrhosis may develop liver cancer[(1)]. Liver transplantation (LT) has emerged as the optimal treatment for cirrhotic patients with HCC because it cures both tumor and underlying cirrhosis. Poor patient selection (excessive tumor burden, unknown tumor biology) made initial results of LT for HCC quite dismal[(2)]. It wasn't until 1996, when Mazzaferro***et al.***[(3)] defined tumor criteria for patient selection (single lesion ≤ 5 cm, or up to 3 lesions ≤ 3 cm each in the absence of tumor vascular invasion or evidence of extra-hepatic metastases) associated with comparable outcome to patients undergoing LT without HCC. Also, they revealed 4 year post-LT survival > 75% and post-LT recurrence rate in the order of 8%. These criteria have since been known as the Milan criteria (MC), and have been adopted worldwide to select HCC patients for LT[(4)]. Patients, who suffered from HCC with or without poor liver function, who were out of the transplant criteria, remained the most difficult group to be treated. Disease could be downstaged or controlled by various anticancer therapies, which might bring them chance of undergoing a curative treatment such as LT [(5)]. HCC downstaging using exclusively transarterial chemoemolization (TACE) or multimodal sequential therapies to meet the conventional criteria for LT among carefully selected patients yields promising results in terms of overall and disease-free survival. In particular, some recent papers have demonstrated that patients successfully downstaged within the MC criteria can achieve a 5-year survival rate comparable to that of patients meeting the abovementioned criteria without requiring downstaging[(6)]**.** TACE has been proven to improve survival and control symptom. It has the advantage of instillation of the chemotherapeutic agent directly into the liver tumor, which was carried by the lipidol, as well as ischemic necrosis induced by arterial embolization. It has been used for unresectable HCC in patients who are awaiting LT as well as those who are not transplant candidates opted for palliative care. Adequate tumor

Received:21/6/2018
Accepted:30/6/2018

necrosis was achieved in the explant liver in the range of 27–57% in patients within Milan criteria. The use of TACE did not only to affect the features of tumor lesions, but also to impact recurrence rate of HCC after LT [(5)].

AIM OF THE WORK

It was to evaluate the outcomes of HCC downstaged patients using transarterial hepatic chemoembolization (TACE) therapy to allow eligibility for liver transplantation.

PATIENTS AND METHODS

Type of Study: Interventional retrospective study. **Study Setting:** The study was conducted at Interventional Radiology Unit at Ain Shams Specialized Hospital. **Study period:** From 2008 to 2017. **Study population:** The study included all the cirrhotic patients who underwent TACE for downstaging of HCC to become eligible for liver transplantation. Total number was twenty seven patients. ***Inclusion Criteria:*** a. Patients with clinical, laboratory and imaging evidence of HCC, b. Patients should be candidates for liver transplantation, yet beyond Milan criteria, c. Patients with Child-Pugh class A or B presentations, d. Prothrombin concentrations of > 50% and platelet counts of > 50,000 per mm3, e. No sex predilection, f. No age predilection. ***Exclusion Criteria:*** a. Patients who underwent other modalities of locoregional treatment for downstaging other than TACE, b. Patients with malignant portal vein thrombosis and/or extrahepatic metastases, c. Patients with Child-Pugh class C presentations, d. Patients with arterio-portal fistulas or extensive portosystemic shunting. **Sampling Method**: Purposive sample, **Ethical Considerations:** all the patients signed an informed consent form and the procedures were done in accordance with the Helsinki declaration of 1975. **The study was approved by the Ethics Board of Ain Shams University. Study Procedures:** Patients have been subjected to: 1. Full history taking with clinical examination, 2. Obtaining laboratory results including alpha fetoprotein, hepatitis markers (HCV Ab, HBsAg and HBcAb), serum bilirubin, serum albumin, complete blood picture, PT, PTT, INR and liver enzymes levels, 3. Having ultrasound done at ultrasound unit of Ain Shams Specialized hospital Radiology department, 4. All patients underwent CT triphasic examination of the liver before and after treatment with TACE. ***Technique of chemoembolization in our facility:*** chemoembolization was carried out at the interventional radiology unit of Ain Shams Specialized hospital. A femoral arterial approach was used with Seldinger technique. The hepatic artery was catheterized with a 5F polyethylene catheter with cobra head configuration (C2 Cordis® USA) or a reverse 5F catheter (Simmonds S2, Cordis® USA). The catheter was advanced into the proximal hepatic artery and an initial subtracted angiogram was obtained after hand injection of 8 cc of nonionic contrast media to detect the tumoral blush, the catheter was further advanced so that the feeding artery of the tumor was super selectively catheterized .TACE was done using a solution of emulsifying oily contrast agent (Lipiodolultrafluid) and chemotherapeutic agents (70–100 mg doxorubicin) mixed with water soluble contrast and saline, using fluoroscopic monitoring, the solution was infused until initial slowing of antegrade blood flow was noted, TACE was then completed by injecting gel foam pledges cut into small pieces mixed with water soluble contrast. Embolization was done under fluoroscopic guidance with serial repeated control angiograms. Evidence of successful embolization was defined by complete stasis of the injected contrast and embolizing material, all patients transplanted received a living donor liver. Explanted livers underwent extensive histologic analysis and staging of HCC, all patients were followed until death or June 2018. In the follow-up period, hepatitis recurrence, HCC recurrence, and patients' survival were analyzed. ***Statistical methods:*** IBM SPSS statistics (V. 25.0, IBM Corp., USA, 2017-2018) was used for data analysis. Date was expressed as mean and median of age in addition to both number and percentage for categorized data.

RESULTS

Total twenty seven, cirrhotic patients underwent TACE for downstaging of HCC to become eligible for liver transplantation, were included in our study. The etiology of cirrhosis and HCC in our patients was primarily Hepatitis C virus which is endemic in our country. Age of the patients ranged from 46 to 63 years old, median age was 55 years. The age at 25th percentile was 52 years and at 75th percentile was 58 years. Only one of the selected patients was a female (3.7%) and the rest 26 patient

were males (96.3 %). All the cases were not eligible for liver transplantation because they were out of Milan criteria, therefore all the cases underwent TACE for downstaging of the tumor to be within the Milan criteria to become fit for liver transplantation. Of the twenty seven patients included in the study thirteen patients were out of Milan criteria because they had three HCC lesions yet one of the lesions or more were larger than 3 cm, eleven patients were out of Milan criteria because there were more than three lesions, the remaining three cases were out because They had a single lesion larger than 5 cm. Alpha feto protein level in the serum of the included patients was measured before and after TACE operation. It ranged from 3.9 to 1422 in the pre therapy measurements and from 3.2 to 545 post therapy with clinically significant reduction of its level following TACE treatment. The patients were categorized according to their child score into Child A (score 5-6), B (7-9) and C (10-15). Number of patients with Child A score was twelve patients. Those with Child score B were nine patients and the least number of the patients had Child score C which was six patients. Statistical relationship between the child score and the alpha feto protein levels of the patients was studied with a p value 0.815 (statistically non significant). After undergoing TACE for downstaging, Patients underwent living donor liver transplantation, then they were followed up for detection of recurrence on the transplanted liver. Four of the twenty seven patients had recurrent HCC (14.8 %). Statistical relationship between recurrence and alpha feto protein level post TACE in patients who had recurrent HCC was studied, yet with no significant statistical relation (p value= 0.244). Also, no statistical significant relationship was found between the Child grade of the patient and the recurrence rate. (p value = 0.92). Two of the patients who had recurrent HCC after transplatation were out of MILAN criteria because of having a lesion or more with a diameter more than 3 cm and the other two patients were out because of having more than three HCC lesions. The size of the HCC lesions was studied and the overall diameter of the lesions was measured and divided into two groups in the examined patients. Group one having an overall diameter ranging from five to seven centimeters: included fifteen patients. Group two having an overall diameter ranging from eight to fifteen centimeters: included seventeen patients. Out of the 15 patients in group one, two had recurrent HCC on the transplanted liver and the other two patients with recurrent HCC were from group two. Thus, no statistically significant relationship was found between the overall diameter of the lesions and the recurrence rate and this might be attributed to the small number of the study population. Two of the included patients in the study were expired early just after liver transplantation due to medical comorbidities.

DISCUSSION

Although LT is a potentially curative treatment for HCC, most patients present at an advanced stage beyond transplant criteria. Thus, the ability to effectively downstage patients confers a definite advantage with respect to access to transplantation[7]. The concept of applying Locoregional treatments to reduce the size of HCC to facilitate resection or LT was first tested by Majno and colleagues from Hospital Paul Brousse, France. A number of more recent studies have formally evaluated down-staging of HCC [8].The majority of these studies have used Milan criteria as the endpoint for down-staging [9]. Down-staging of HCC has been identified as a priority for research in the field of LT for HCC in a National Cancer Institute consensus conference [10]. Downstaging allows for patients who do not fit the MILAN criteria to be considered for transplant if they sustain a good response. It also allows for selection of those patients who carry a favorable biology but poor morphology. Currently there is no evidence in the literature that patients who respond to downstaging protocols do worse than patients who originally were eligible for transplant without any intervention. Actually in most of the reported series, the posttransplant outcomes are similar between both groups with a 5-year overall survival reaching up to 94 % and a 5-year disease-free survival up to 75 % [11,12]. In this retrospective study, we analyzed the clinical results and recurrence rate of 27 patients who did not fulfill Milan selection criteria who underwent TACE followed by LDLT. With a median follow-up of 30 months, the recurrence rate for our study population was14.8%, which are higher yet comparable to the results reported in patients who met the Milan selection criteria (2.1 % recurrence rate in 94 patients). This higher recurrence rate may be attributed to lack of upper limit in size and number of tumors in patients not meeting the Milan criteria to undergo downstaging.

Most of studies in the literature had no upper limit which agreed with our study, yet two authors have provided inclusion criteria for patients for downstaging and yielded very similar recurrence results in both groups (patients who met the Milan criteria and patients who did not) [13,14]. Analysis of the factors associated with response to treatment showed that both downstaging and total necrosis of the tumor occurred more frequently in patients with solitary lesions. This is in agreement with previous reports as ***Majno et al.*** and ***Yao et al.*** Downstaging occurred more frequently in patients with largest tumor > 3 cm, which goes against the commonly held belief that TACE is ineffective in patients with large tumors. In fact, most of these studies evaluated the effect of palliative TACE in patients with inoperable disease rather than in a preoperative setting. Other investigators as Wiesner ***et al.*** and Yao ***et al.*** have reported marked size reduction after TACE in patients with large tumors[13, 14]. We observed post transplantation HCC recurrence in four patients after down-staging, but the median follow-up of 30 months after LT may be too short to fully ascertain the recurrence risk. The number of patients with ≥4 tumor nodules is small, and more data are needed. The low rate of poorly differentiated tumor grade and vascular invasion in the explant is surprising, but this observation may reflect selection of tumors with more favorable biology before LT, in accord with the fundamental principle behind the down-staging process. There are technical and anatomical factors, in addition to tumor biology, that influence initial response to loco-regional therapy, but the likelihood of tumor progression despite treatment is expected to be higher in those with microvascular invasion and other unfavorable tumor characteristics. High AFP of > 1000 ng/mL was a significant predictor of treatment failure. There is growing evidence that this degree of elevation in the AFP level predicts a greater risk of tumor recurrence after LT[14].High AFP may be a marker for vascular invasion or extrahepatic disease that escapes detection by conventional imaging techniques. High AFP has also been shown in a plethora of studies to be predictive of worse prognosis after LT[15].Although the best AFP cut-off in predicting prognosis after LT is still subject to debate, an AFP >1000 ng/mL was shown in 2 recent studies to be associated with worse outcome after LT for HCC within Milan criteria [16, 17].The U.S. national conference proposed adding AFP > 1000 ng/mL as an exclusion criterion for LT unless the AFP level decreases to < 500 ng/mL after down-staging treatments[18]. Almost all of our patients showed a marked response to pretransplantation TACE; 97% of the patients had either a complete necrosis or at least a greater than 50% size reduction in the explanted liver. In contrast, two comparable trials showed 50% tumor reduction in only about half of the patients [19,20]. The very high response rate is possibly explained by repeated TACE sessions in a short period of time to achieve maximal necrosis. Our results as regards the recurrence rate of HCC in the follow up period (14.8 %) was comparable to results of other authors in the literature as Barakat***et al***who reported recurrence rate post liver transplantation of 14.2 % in 14 patients and Jang ***et al.*** who reported recurrence rate of 29.7 % in 37 patients [9, 12].

CONCLUSION

In conclusion, TACE appears to be useful in the management of HCC associated with cirrhosis before liver resection or transplantation. TACE contributes to accurate staging of the intrahepatic disease, and response to treatment with downstaging or total necrosis of the tumor, obtained in near all treated cases, was accompanied by a benefit in survival. In liver resection, TACE is indicated particularly for tumors exceeding the Milan criteria, which are more likely to respond with downstaging, resulting in improved surgical access and resectability. We report excellent post-transplant outcome after successful down-staging of HCC prior to LT to meet the Milan Criteria. In spite of limitations of the present study, the overall low rate of HCC recurrence after LT and the low incidence of either poorly differentiated grade or micro-vascular invasion in the liver explant support the role of down-staging in the selection of patients with tumors of more favorable biology that respond to LRT and also do well after LT.

CONFLICTS OF INTEREST

There are no conflicts of interest.

REFERENCES

1- **Gomaa A, Allam N, Elsharkway A, El Kassas M and Waked I (2017):** Hepatitis C infection in Egypt: prevalence, impact and management strategies. Hepat Med., 9: 17–25.

2- Saidi RF and Kenari SH(2017): Liver Transplantation for Hepatocellular Carcinoma: Past, Present and Future. Middle East J Dig Dis., 5(4): 181–192.

3- Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozetti F, Montalto F, Ammatuna M, Morabito A and Gennari L (1996): Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med.,334(11):693-9.

4- Elshamy M, Aucejo F, Menon KV, and Eghtesad B (2016): Hepatocellular carcinoma beyond Milan criteria: Management and transplant selection criteria. World J Hepatology, 8(21): 874–880.

5- She WH and Cheung TT (2016): Bridging and downstaging therapy in patients suffering from hepatocellular carcinoma waiting on the list of liver transplantation. Trans Gastroenterol Hepatology. J., 1: 34.

6- Pompili M, Francica G, Ponziani FR, Iezzi R, and Avolio AW (2013): Bridging and downstaging treatments for hepatocellular carcinoma in patients on the waiting list for liver transplantation**.** World J Gastroenterol. J., 19(43): 7515–7530.

7- Lewandowskia RJ, Kulik LM, Riaz A, Senthilnathana S, Mulcahy MF, Ryu RK,Ibrahima SM, Sato KT, Bakerd T, Millera FH, Omarya R, Abecassisd M and Salema R (2009): Role of TACE in Patients with Hepatocellular Carcinoma before Liver Transplantation. American Journal of Cancer Prevention, 4 : 2 (23-25)

8- Yao FY, Breitenstein S, Broelsch CE, Dufour JF and Sherman M (2011): Does a patient qualify for liver transplantation after the down-staging of hepatocellular carcinoma? Liver Transpl., 17 (2): 109-16.

9- Barakat O, Wood RP, Ozaki CF, Ankoma-Sey V, Galati J, Skolkin M, Toombs B, Round M, Moore W andMieles L (2010): Morphological features of advanced hepatocellular carcinoma as a predictor of downstaging and liver transplantation: an intention-to-treat analysis. Liver Transpl., 16(3):289-99.

10- Thomas MB, Jaffe D, Choti MM, Belghiti J, Curley S, Fong Y, Gores G, Kerlan R, Merle P, O'Neil B, Poon R, Schwartz L, Tepper J, Yao F, Haller D, Mooney M and Venook A (2010): Hepatocellular carcinoma: consensus recommendations of the National Cancer Institute Clinical Trials Planning Meeting. J ClinOncol., 28(25):3994-4005.

11- Chapman WC, Majella MB, Stuart JE, Vachharajani N, Crippin JA and Anderson CD (2008): Outcomes of neoadjuvant transarterial chemoembolization to downstage hepatocellular carcinoma before liver transplantation. Ann Surg., 248(4):617–625.

12- Jang JW, You CR, Kim CW, Bae SH, Yoon SK, Yoo YK *et al*.(2010): Benefit of downsizing hepatocellular carcinoma in a liver transplant population. Aliment PharmacolTher.,31(3):415–423

13- Wiesner RH, Freeman RB and Mulligan DC(2004): Liver transplantation for hepatocellular cancer: the impact of the MELD allocation policy. Gastroenterology J. ,127(1):S261-S267.

14- Yao FY, Xiao L, Bass NM, Kerlan R, Ascher NL and Roberts JP (2007): Liver transplantation for hepatocellular carcinoma: validation of the UCSF expanded criteria based on pre-operative imaging. Am J Transpl., 7:2587-2596.

15- Hakeem AR, Young RS, Marangoni G, Lodge JPA, and Prasad KR (2012): Systematic review: the prognostic role of alpha-fetoprotein following liver transplantation for hepatocellular carcinoma. Aliment PharmacolTher., 35:987–999

16- Duvoux C, Roudot-Thoraval F, Decaens T, Pessione F, Badran H, Piardi T*et al*. (2012): Liver transplantation for hepatocellular carcinoma: a model including α-fetoprotein improves the performance of Milan criteria. Gastroenterology, 143:986–984.

17- Hameed B, Mehta N, Sapisochin G, Roberts JP and Yao FY (2014): Alpha-fetoprotein >1000 ng/mL as an exclusion criterion for liver transplant in patients with hepatocellular carcinoma meeting Milan criteria. Liver Transpl J., 20:945–951.

18- Pomfret EA, Washburn K, Wald C, Nalesnik MA, Douglas D, Russo M*et al.* (2010): Report of a national conference on liver allocation in patients with hepatocellular carcinoma in the United States. Liver Transpl., 16:249–251.

19- Harnois DM, Steers J, Andrews JC, Rubin JC, Pitot HC, Burgart L *et al.* (2008): Preoperative hepatic artery chemoembolization followed by orthotopic liver transplantation for hepatocellular carcinoma. Liver Transpl Surg., 5:192-199.

20- Majno PE, Adam R, Bismuth H, Castaing D, Ariche A, Krissat J *et al.* (2006): Influence of preoperative transarteriallipiodol chemoembolization on resection and transplantation for hepatocellular carcinoma in patients with cirrhosis. Ann Surg.,226:688-701.