Hepatocellular Carcinoma Treatment with Transarterial Chemoembolization: Complications and Impact on Size of Esophageal Varices

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Abstract: Introduction: Transarterial chemoembolization (TACE) is an optimal treatment for HCC patients with unresectable intermediate stage hepatocellular carcinoma (HCC) without significant hepatic synthetic dysfunction. TACE may be associated with many injurious complications although it may be associated with increased survival in some patients. TACE produces elevation in portal blood flow and increased intra-variceal pressure and in rare instances may precipitate bleeding from esophageal varices in patients with coexisting portal Hypertension. This study aimed to detect TACE complications with especial emphasis in changes in size of esophageal varices after treatment. **Patients and Methods:** Our study was conducted on 77 naïve HCC patients with small sized esophageal varices with no history of upper gastrointestinal bleeding or prophylactic beta-blocker treatment. These HCC patients were diagnosed according to the American Association for the Study of Liver Diseases 2010 (hepatic focal lesion with CT or MRI criteria of HCC wash in arterial phase and washout in portovenous- delayed phases). The patients were conducted on liver function tests, renal functions tests, INR, CBC and AFP and viral markers. They were treated with TACE according Barcerlona–Clinic Liver Cancer. Upper GI- endoscope was done in these patients within one week before TACE and 3 months after TACE. **Results:** Complications within 3 months after TACE were recorded as follow: Postembolization syndrome is seen in 65(84.1%) out of 77 cases, portal vein thrombosis was developed in 9 (11.68%) from 77 patients, hepatic decompansation in 6(7.79%) patients, non-responders to one session of TACE was detected in 39 (58.2%)of cases and variceal bleeding were recorded in 4 (5.19%) cases out of 77 HCC cases. Renal impairment was detected in 5 HCC cases but with careful fluid replacement improvement was noticed in 4 of them. Rare complications such hepatic abscess (one patient) and arteriovenous fistula in (one patient) were seen. 10 (12.98 %) HCC patients included in our study had esophageal varices changed from small to large sized esophageal varices and the rate of this change was a statistically significant P<0.03). In our study variceal changes from small to large varices were obviously detected in patients who had developed portal vein thrombosis (5 cases out of 9 cases) , hepatic decompensation (4 cases out of 6 patients) (p<0.005).**Conclusion:** TACE is associated with injurious complications such as PVT, hepatic decompensation and increased esophageal size thus careful selection of HCC patients who will be treated with TACE is mandatory to avoid injurious complications especially hepatic decompensation and GI-bleeding.Disclosure of Interest: None Declared

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1. Introduction

Worldwide, HCC is the 5th most common cancer and the 3rd cause of cancer related mortality. Chronic HBV and hepatitis C are the main predisposing factors for liver cirrhosis and HCC development **(Elserag, 2012).** Liver cirrhosis is considered a precancerous condition. Among HCC patients, the prevalence of cirrhosis has been estimated to be 85%-95% **(kanwal et al., 2011)**and the rate of HCC incidence in cirrhotic patients has been shown to be 2%-4% per year **(El-Serag., 2011).**

TACE or bland TAE are optimal indications for the treatment of patients with unresectable HCC or unsuitable conditions for locoregional ablations or used asa bridge to liver transplantation provided that they have preserved liver functions and no extrahepatic metastasis. The aim of using TACE in these conditions is to increase survival in these patients **(Julie et al., 2017).** Portal vein occlusion, extensive infiltration of both lobes, advanced liver disease, severe comorbidities and unsuitable technical conditions such as untreatable A-V shunt are considered absolute contraindications for TACE **(Raoul, 2011).** Prognosis of HCC depends on the stage of cancer and on the underlying degree of hepatic dysfunction **(Lencioni et al., 2010**).

A total bilirubin level above 3 mg/mL is a relative contraindication to TACE as the risk of hepatic necrosis and abscess formation is increased **(Tabrizian et al., 2014**).

TACE can increase portal pressure through:(i) decline in arterial blood flow and this leads to compensatory increase in portal blood flow (ii) increasing arterial blood flow from the left gastric artery into esophageal varices; (iii) endocellular dysfunction and proinflammatory response that occur after TACE as TACE can induce ischemia and increase in vascular tone. All of these changes are transient and starts to appear early after TACE **(Okada et al., 2001, Spahr et al., 2003).**

This study is aimed to evaluate the complications of TACE with especial emphasis on changes of esophageal variceal size before and after TACE.

2. Patients and Methods

Our study was conducted on 77 naïve hepatocellular carcinoma patients with small sized non risky esophageal varices (F1) with no history of upper gasterintestinal bleeding or prophylactic beta-blocker treatment. They were selected from outpatient clinics of Hepatology department of National Liver Institute after obtaining a written consent. These HCC patients were diagnosed according to the American association for the study of liver diseases 2010 (hepatic focal lesion with CT or MRI criteria of HCC wash in arterial phase and washout in portovenous- delayed phases) **(Bruix and Sherman, 2010).**

These patients were conducted on liver function tests, renal functions tests, INR, CBC and AFP and viral markers. These patients were treated with TACE according to updated Barcelona staging system for HCC (**Bruix and Sherman, 2011).** (stage B ; patients with intermediate stage HCC, HCC patients with single or multiple focal lesions, HCC patients with child A or B with portal hypertension, Patients with performance state I, II). HCC patients not amenable to surgical resection or radiofrequency ablation, HCC patients with prior variceal bleeding, distant metastasis, portal vein thrombosis and advanced comorbid conditions were excluded.

Upper GI- endoscope was done in these patients within one week before TACE and 3 months after TACE to determine any changes in size OV. Esophageal varices were graded into 3 grades according to the Japanese Research Society for Portal Hypertension classification is as follows: 1- Straight (F1) 2-Enlarged, tortuous (F2) 3-Very large varices (F3**) (Beppu et al.,1981**).Those who had OV grade F1 are considered small OV and those with grade F2 or F3 are considered large varices.

IV) Transarterial chemoembolization (TACE) Procedure:

The procedure involved gaining percutaneous transarterial access by the Seldinger technique to the hepatic artery with an arterial sheath, usually by puncturing the common femoral artery in the right groin and passing a catheter guided by a wire through the abdominal aorta, through the celiac trunk and common hepatic artery, and finally into the branch of the proper hepatic artery supplying the tumor. An iodized oil-doxorubicin hydrochloride emulsion was injected into the feeders. Once sluggish flow started to appear, gelatin sponge particles were administered into the feeders until complete blood flow was stopped. The physician removed the catheter and applying pressure to the entry site. The patient was often kept overnight for observation and was likely discharged the following day.

Follow-up after TACE:

Patients were followed monthly for 3 months and those who survived to the date of follow up were included in our series. They were followed clinically, the needed laboratory and radiological evalution were done according to the reported complication. AFP, liver function test, CBC, INR, renal function tests were done monthly for 3 months. Patients were followed up after intervention by dynamic CT scan or MRI to document response for treatment. The reported complications were assessed and treated. In our study, Tumor response to TACE was evaluated one month after TACE procedure with CT according to amended modified Response Evaluation Criteria in Solid Tumors (m-RECIST) guidelines. Complete response (CR) is the disappearance of any arterial enhancement in all target lesions; a partial response (PR) is $\geq$ 30% decline in the enhancement of diameters of the viable portion of target lesions, progressive disease (PD) is an increase of $\geq$ 20% in the sum of the diameters of viable target lesions, taking as reference the smallest sum of the diameters of viable lesions recorded since the treatment started or ; stable disease (SD) is any case that does not identical for classification as either a PR or PD **(Llovet et al., 2008**). In our series, HCC patients with CR and PR are considered responders but those with SD or PD are considered non responders to treatment with TACE.

Statistical analysis:

The data were collected, tabulated and analyzed by SPSS version 17 on IBM compatible computer. Two types of statistics were used. First, descriptive statistical tests included percentage, mean and standard deviation. Second, analytical statistical tests included Chi-square, Fisher Exact test, Z test, Mann Whitney U test, Paired t test and Wilcoxon Signed Rank. P value was considered significant if it is <0.05.

3. Results

Among 488 HCC patients presented to Hepatology department, 126 patients were fit for

TACE from which 77 patients had small OV and included in our study and were followed up. Demographic data (age, gender, past history and family history) of the studied 77 HCC patients were presented in **table 1.**

In our series, HCV infection is the main cause of liver cirrhosis and HCC followed by HBV infection and dual infection with HBV and HCV infection. The laboratory investigations before and 3 month after TACE in the studied HCC cases were shown in t**able 2**.There were no statistical differences before and after TACE regarding, serum bilirubin, AST, ALT, INR, hemoglobin, total leucocytic count, platelets (p value > 0.05). But there were highly significant difference among the studied HCC cases regarding serum AFP and serum albumin (p value <.05).The ultrasound findings regarding portal vein diameter and patency were presented in **table 3**. In regarding to portal vein patency before and after TACE, there were 9 (11.6%) patients had portal vein thrombosis after TACE witha statistically significant differences before and after TACE p value < 0.05.

The reported complications after TACE were demonstrated in **table 4**. The reported post-TACE complications were postembolization syndrome in 65 (84.4%) patients, renal impairment in 5 (6.4%) patients with improvement of 4 of them with adequate hydration. In addition portal vein thrombosis was detected in 9 (11.6%) patients. Decompensation of liver functions in 6 (7.7%) patients.Post-TACE ascites was developed in 5 (6.5%) cases. One (1.3%) patient had developed arteriovenous fistula and also one (1.3%) patient had developed liver abscess. Esophageal varecial bleeding occurred in 4 (5.19%) patients. 10 (12.9%) HCC patients had OV changed from small sized (F1) to large sized OV (F2-F3) after 3 months of TACE with a statically significant difference. The changes in OV size after TACE was shown in **table 5**. Small sized esophageal varices were present in 77 (100%) of HCC patients before TACE and in 67 (87.1%) HCC patients after TACE. Thus 10 (12.9%) of these patients had OV converted from small to large sized esophageal varices and the rate of this change is a statistically highly significant P value (0.003).

According to Child–Turcotte–Pugh classification, 43 (55.8%) patients were Child A, 34 patients (44.2%) were Child B before HCC treatment with TACE. After HCC treatment with TACE 6 (7.7%) patients out of the total 77 patients became decompensated (2 patients from Child A and 4 patients from Child B). Child–Pugh before and after TACE had no effect on size of OV after TACE and was illustrated in **table 6.**

In the decompensated 6 HCC cases, 4 patients had esophageal varices converted from small to large sized varices after TACE. In our study variceal changes from small to large sized esophageal varices were obviously detected in patients who had developed portal vein thrombosis and hepatic decompensations with a highly statistically significance. 5 (55.5%) cases out of 9 HCC cases with post-TACE portal vein thrombosis had OV converted to large sized OV (p <0.05). Also, regarding to post-TACE hepatic decompensation 4 (66.6%) cases out of 6 patients had OV converted to large sized OV (p<0.05). This is shown in **table 7**.In our study, there were 34 (44.2%) HCC patients responding to one session of TACE. However the HCC non responding patients were 43 (55.8%). This is represented in figure I.

Table 1: Demographic data of the studied HCC group

Demographic data	The studied cases N = 77	
Age Mean ±SD Range	56.92±6.37 42 – 74	
	No	%
Gender Male Female	 60 17	 77.9 22
Diabetics	12	15.5
Hypertensive	5	6.4
Bilharziasis and treated	10	12.9
Smoking	21	27.2
Positive family history	6	7.7
Positive HbsAg	2	2.59
Positive HCV Ab	74	96.1
Dual HCV and HBV infection	1	1.29

SD = standard deviation

Table 2: Laboratory results pre and 3 months post TACE in HCC cases

Mean ±SD	Pre-TACE N=77	Post-TACE N=77	P value
Bilirubin	1.41±0.39	1.48±0.90	0.21
AST	38.49±24.65	41.21±31.88	0.69
ALT	57.32±48.78	58.22±49.09	0.72
Albumin	3.17±0.26	3.1±0.3	0.04
INR	1.38±0.21	1.35±0.22	0.26
creatinine	0.92 ± 0.19	1.26±0.45	0.45
BUN	30.38±4.91	35.78±17.75	0.02
Hb	11.67±0.84	11.66±0.94	0.94
Platelets	102.13±49.94	104.6±34.1	0.39
TlC	6717.03± 3134.	5937.2 ± 3754.5	> 0.05
AFP	310.09±364.95	140.04±181.36	<0.001*

Data was expressed as mean and SD (standard deviation).

Table 3: Ultrasound findings of portal vein status pre and 3 months post TACE.

	The studied groups N =77		Test	P value
	Pre -TACE	3 months post TACE		
Portal vein diameter Mean ±SD Range	 12.78±1.72 11-16	 12.88±2.31 12-21	Paired t test 0.33	 0.74
Prtal vein patency Patent Thrombosed	 77(100) 0 (0.0)	 68 (88.3%) 9 (11.6 %.)	X2 10.69	 0.001

Table 4: Complications of TACE among the HCC patients.

	The studied cases N = 77	
	No	%
Post embolization syndrome	65	84.4
Renal impairment	5	6. (4 cases improved)
Portal vein thrombosis	9	11.6
Hepatic decompensation	6	7.7
A.V fistula	1	1.2
Liver abscess	1	1.2
Ascites	5	6.49
Esophageal variceal bleeding	4	5.19
OV changes from small to large varices.	10	12.9

Table 5: Comparing esophageal variceal changes pre and 3 months post TACE in the studied HCC cases

Small size OV		Large sized OV	Test (p value)
Pre TACE	3 months post TACE	Rate of conversion from small to large OV	Z test
77 (100)	67 (87.0)	10 (13.0)	2.95 (0.003)

Table 6: Pre and post TACE changes of OV regarding child–Pugh classification.

Child classification	**Pre–TACE N=77**	**Post TACE N=77**	**Post-TACE changes of OV from small to large sized O.V N=10**	**(P- value)**
	No (%)	No (%)	No (%)	
A **B** **C**	43 (55.8) 34 (44.1) 0	41 (53.2) 30 (38.9) 6 (7.7)	2 (2.5) 4 (5.1) 4 (5.1)	FE 0.77 (0.50)

Table 7: Relation between converting from small to large OV in HCC cases in 3 months post TACE and complications

	Conversion from small to large OV (3 months post TACE)		Test (p value)
	Small sized OV N = 67	Large sized OV N = 10	
	N (%)	N (%)	
PV thrombosis (9) cases Positive Negative	 4 (5.9) 63 (94)	 5 (55.5) 4(44.4)	FE 4.75 (0.03)
Decompensation (6) cases Positive Negative	 2 (3.0) 65 (97.0)	 4 (66.6) 2(33.3)	FE 16.69 (0.002)

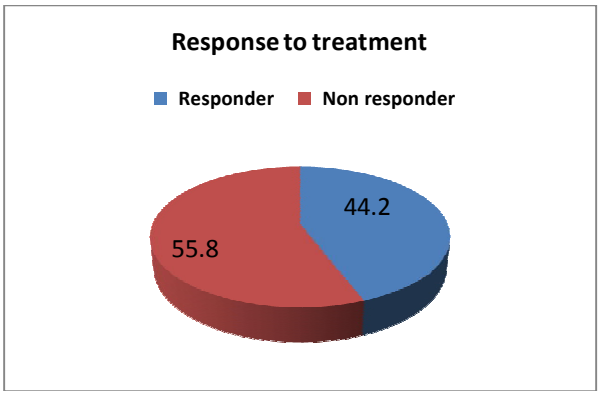

Figure (1): Show responders and non responders to one session of TACE

4. Discussion

Hepatocellular carcinoma is one of the most prevalent cancers worldwide **(Yim et al., 2015).** It ranks as the fifth most common cause of cancer in men and the seventh one in women **(Bosetti et al., 2014**) and is the second-most leading cause of cancer-related mortality in the world (**Rojpibulstit et al., 2014**). The prevalence of cirrhosis among patients with HCC has been estimated to be 85%-95% **(kanwal et al., 2011**) and the HCC incidence rate among patients with cirrhosis has been shown to be 2%-4% per year **(El-Serag., 2011**).Prognosis of HCCdepends on the stage of cancer and on the underlying degree of hepatic dysfunction **(Lencioni et al., 2010).**In HCC patients, about one third of HCC mortality is due to hepatic failure and 10% is due to GI bleeding **(Yu et al., 2016).**Early detection of major complications following HCC treatment with TACE is of precious importance asmortality is high in these conditions. In a study by Tu et al, 2016 found that the mortality rate of major complication following TAE/TACE was 16.7% in their study **(Tu et al., 2016).**

This study was aimed to detect TACE complications with especial emphasis in changes in variceal size after treatment with TACE. This study involved a total of 77 compensated cirrhotic patients with hepatocellular carcinoma of whom 60 (78%) were males and 17 (22%) were females. In the present study viral infections with hepatitis C and/or B were the principle causes of liver cirrhosis and HCC. High seropositivity regarding hepatitis markers was proved in this series (Anti HCV antibodies were found in 74 (96.7%) cases patients. However HBs Ag was positive in 2 (3.3%). patients. Co-infection with HCV and HBV was present in one patient. Therefore, cirrhosis is a major risk factor for HCC development. More efforts are needed to detect HCC at a suitable early treatable condition for good HCC treatment as HCC management is affected by the underlying liver injury **(Julie et al., 2017).**

There is no debate that HCC and portal hypertension could occur coincidently. This means that HCC can predispose to worsening portal hypertension, and portal hypertension can predispose to worsening HCC. In some HCC cases, the increase in HVPG (sinusoidal pressure) is through the development of arteriovenous shunting within the tumor. The macroscopic or even microscopic portal vein invasion can lead to pre-hepatic portal hypertension and hence the development of OV **(Tandonand Garcia-Tsao., 2006).** In many HCC cases PVT associated with development of portal hypertension can increase portal vein diameter larger than 15 mm **(Zwiebel, 1995)**.

Postembolization syndrome (PES) is seen 65 (84.1%) of HCC cases in our series. PES is reported to occur in about 55- 90% of HCC cases after TACE **(Leung et al., 2001) (Dhand and Gupta 2011).**Portal vein thrombosis was developed in 9 (11.68%) from 77 HCC patients. Portal vein tumor thrombus (PVTT) is negatively associated with survival of HCC patients (**Tandon and Garcia-Tsao, 2009)** and it is traditionally considered as the contraindication for TACE **(Bruix and Sherman, 2011)** because the presence of PVTT potentially induces the development of acute liver failure or infarction after TACE**.**

Hepatic decompensationis detected in 6 (7.79%) patients. Decompensation as a result of TACE was seen in 7.5% cases in a study by **(Tasneem et al., 2013).** Deterioration of liver functions and increase in total bilirubin are usually seen after TACE and are present with collateral damage. Increasing ascites or its development is considered one of the indirect surrogates of increasing portal hypertension and deterioration of portal hemodynamics (**Lake-Bakaar et al., 2014**).

In the present study variceal bleeding after one session of TACE in HCC cases with small sized OV was recorded in 4 (5.19%) of cases. In various reports variceal bleeding after TACE is reported in 6-28% of cases. The morbidity and mortality are the main drawbacks of variceal bleeding in these patients **(Giannini et al, 2006, Kadouchi et al, 2007)(Elia et al., 2011**).

10 (12.98 %) HCC Patients included in our study had esophageal varices changed from small to large sized esophageal varices and the rate of this change was a statistically significant P<0.03). This is obviously detected in patients who had developed portal vein thrombosis (5 cases out of 9 cases) and hepatic decompensations (4 cases out of 6 patients) (p<0.005).This indicates that changes in OV after

TACE in our series is through direct and indirect effects and are mainly by the indirect effects through the development of portal vein thrombosis and hepatic decompensation after TACE. Aggressive portal vein tumoral thrombosis occluding portal vein can result in portal hypertension and further deterioration of hepatic functions **(Minagawa and Makuuchi, 2006) (Aldrighetti et al., 2009**).Thrombotic occlusion of the portal vein increases the portal pressure and the resulting esophageal gastrointestinal bleeding can be fatal. The direct effect is through the increase of portal blood flow after TACE. These effects can explain the elevation of variceal pressure described in some patients after TACE.

Persistentrenal impairment was detected in one patient after TACE. This appears to be through the toxic effects of contrast and chemotherapeutic agents **(Huo et al., 2004).**After TACE procedure, hepatic abscess was seen in one patient 1.2% and also arteriovenous fistula was seen in one patient. The described incidence of liver abscess appears low after TACE procedure (0.1–4.5%) in many studies **(Song 2001, kim 2001, Xia 2006).** Moreover LV and his colleagues found that liver abscesses incidence were a 0.58% per patient and 0.19% per procedure **(LV et al, 2016).** The difference in incidence of liver abscess following TACE among studies is related to heterogenousity in the selected HCC patients treated with TACE, number of HCC patients and variation in chemoembolization **(Johnson et al., 2011).**

In our study, Tumor response to TACE was evaluated at 1 month after TACE procedure with CT according to amended Response Evaluation Criteria in Solid Tumours (RECIST) guidelines. In our study, non-responders to one session of TACE were detected in 39 (58.2%) patients of cases. There were 34 (47.8%) responders to one cession of TACE in our study. In a study by Bonekamp and his colleuges showed response to TACE was 42.25% according to RECIST criteriabutwas 60.5% according to modified RECIST criteria **(Bonekamp et al., 2011**).Also in a study by Jeong and his colleuges, they found the CR to one and two sessions of TACE were 60% and 15% in their study respectively **(Jeong et al., 2017**). Also, after TACE, CT showed tumor response in 55% of HCC patients who exceeded the Milan criteria and underwent OLT after TACE in a study by **Bargellini et al. (2010).**

In our study the mean serum AFP was decreased significantly in HCC after TACE. The decline of serum AFP level after HCC treatment can predict the response to treatment, survival and the prognosis of HCC **(Riaz et al., 2009) (Tsai et al , 2010) (Kohles et al., 2012).**TACE produces tumor necrosis in many HCC patients and this is subsequently followed by a decline in AFP concentration after the procedure **(Shin, 2009)**.

In conclusion: TACE for HCC cases may be associated with some serious complications including increasing size of esophageal varices, portal vein tumor thrombosis and hepatic decompensations Thus careful selection of HCC patients that will be treated with TACE is mandatory and early treatment of these complications may be lifesaving.

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