RESEARCH ARTICLE

Conventional versus Doxorubicin-Eluting Beads Transarterial Chemoembolization for Unresectable Hepatocellular Carcinoma: a Tertiary Medical Centre Experience in Malaysia

F Abdul Rahman[1], J Naidu[1]*, CS Ngiu[1], Y Yaakob[2], Z Mohamed[2], H Othman[3], R Jarmin[3], MH Elias[4], N Abdul Hamid[4,5], N Mohd Mokhtar[4], RA Raja Ali[1]

Abstract

Background: Hepatocellular carcinoma (HCC) is a common cancer that is frequently diagnosed at an advanced stage. Transarterial chemoembolisation (TACE) is an effective palliative treatment for patients who are not eligible for curative treatment. The two main methods for performing TACE are conventional (c-TACE) or with drug eluting beads (DEB-TACE). We sought to compare survival rates and tumour response between patients undergoing c-TACE and DEB-TACE at our centre. Materials and Methods: A retrospective cohort study of patients undergoing either treatment was carried out from January 2009 to December 2014. Tumour response to the procedures was evaluated according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST). Kaplan-Meier analysis was used to assess and compare the overall survival in the two groups. Results: A total of 79 patients were analysed (34 had c-TACE, 45 had DEB-TACE) with a median follow-up of 11.8 months. A total of 20 patients in the c-TACE group (80%) and 12 patients in the DEB-TACE group (44%) died during the follow up period. The median survival durations in the c-TACE and DEB-TACE groups were 4.9 ± 3.2 months and 8.3 ± 2.0 months respectively (p=0.008). There was no statistically significant difference noted among the two groups with respect to mRECIST criteria. Conclusions: DEB-TACE demonstrated a significant improvement in overall survival rates for patients with unresectable HCC when compared to c-TACE. It is a safe and promising approach and should potentially be considered as a standard of care in the management of unresectable HCC.

Keywords: Transarterial chemoembolization - conventional - doxorubucin-eluting beads - hepatocellular carcinoma

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most frequently diagnosed cancer worldwide and the second most common cause of cancer death in the world (Torre et al., 2012). The GLOBOCAN database recently reported that 70-90% of primary liver cancers occurring worldwide are HCC (Torre et al., 2012). HCC is reported as one of the cancers with the highest mortality accounting for 1% of deaths worldwide (Kew MC, 2010).

HCC is a complex disease associated with many risk factors. Infection with the Hepatitis B Virus (HBV) and Hepatitis C Viruses (HCV) are the most common risk factors for HCC (Lafaro et al., 2015). Other risk factors include alcoholic liver disease and non-alcoholic steatohepatitis (El-Serag, 2012). It is reported that aflatoxin-contaminated food, diabetes, obesity, certain hereditary conditions such as hemochromatosis, and various metabolic disorders are additional risk factors that can contribute to HCC (Sherman, 2010).

The diagnosis of HCC depends mostly on non-invasive criteria for example using computed tomography and dynamic contrast magnetic resonance imaging (MRI) (Pascual et al., 2016). Unfortunately, the majority of patients with HCC are diagnosed at an advanced stage thereby precluding curative therapies like hepatic resection and radiofrequency ablation (RFA) (Au et al., 2015; Kudo, 2015; Schultheiss et al., 2015; Sasaki Y, 2015). Transarterial chemoembolization (TACE) is often used as a palliative modality of treatment for patients with unresectable HCC (Brown et al., 2006; Lencioni et al., 2012; Meza et al., 2012; Boulin et al., 2015; Ciria et al., 2015; Wang et al., 2015; Zu et al., 2015). Conventional TACE (c-TACE) involves selective delivery of a chemotherapeutic agent

*[1]Gastroenterology Unit, Department of Medicine, [2]Endovascular and Interventional Unit, Department of Radiology, [3]Hepatobiliary Unit, Department of Surgery, [4]Department of Physiology, Faculty of Medicine, Universiti Kebangsaan Malaysia Medical Centre, [5]Faculty of Medicine and Health Sciences, Universiti Sains Islam Malaysia, Kuala Lumpur, Malaysia *For correspondence: jeevinesh@gmail.com*

such as cisplatin in lipiodol, followed by injection of an embolising agent into the vessel supplying the liver tumour (Kawahara et al., 2015; Lo et al., 2002; Song et al., 2011). It is the recommended first line treatment for patients with unresectable HCC as stated in the Barcelona Clinic Liver Cancer (BCLC) guidelines (Bruix J et al., 2001; Llovet et al., 2002). TACE with drug eluting-beads (DEB-TACE) is designed to improve treatment efficacy by occluding the feeding vessels of the tumour and gradually releasing the anti-cancer drugs in order to create a controlled localised delivery system (Arabi et al., 2015; Lammer et al., 2010). Recent randomised controlled trials have shown statistical survival benefits and improved therapeutic efficacy of TACE especially DEB-TACE in unresectable HCC over supportive care or systemic chemotherapy (Lammer et al., 2010; Chan et al., 2015; Yang et al., 2015).

The purpose of this study was to evaluate the overall survival rates of patients with unresectable HCC following c-TACE versus DEB-TACE and to determine the treatment response and adverse events with each of these modalities.

Materials and Methods

Study design:

This is a retrospective cohort analysis of patients diagnosed with unresectable HCC, treated with either c-TACE or DEB-TACE from January 2009 to December 2014 at the National University of Malaysia Medical Centre. Diagnosis of HCC was mainly based on typical radiological findings with or without alpha-fetoprotein levels according to the Barcelona criteria (El-Serag, 2012). Liver biopsy was performed in selected cases where the diagnosis was indeterminable. All patients were discussed at our multidisciplinary team (MDT) meeting involving interventional and diagnostic radiologists, gastroenterologists, and hepatobiliary surgeons. Following a session of TACE, a repeat imaging modality was performed after 1 month (CT or MRI) and the case discussed at the MDT. If the patient remained in BCLC stage A or B then a repeat TACE was scheduled 2 to 4 weeks after the follow up imaging.

All patients eligible for TACE after 2011 were offered DEB-TACE as this was the year during which DEB was available at our centre. Inclusion criteria were patients with (a) unresectable HCC (b) HCC recurrence post-resection, RFA or c-TACE, (c) patients who had declined curative therapy, (d) Performance status: Eastern Cooperative Oncology Group (ECOG) Score < 3 and (e) Child-Turcotte-Pugh's (CTP) Class A or B. Patients were mostly of BCLC Stage B however, some patients of BCLC Stage A were included if RFA was not possible due to tumour location, or if their liver reserve was deemed insufficient for resection. Liver biochemistry for enrolment included bilirubin not more than 50 μmol/L, aspartate aminotransferase and alanine aminotransferase < 270 IU/L, serum creatinine not more than 180 umol/L and platelet count more than 50,000/mm3.

Patients with extra hepatic metastasis, portal vein invasion, arterioportal shunts, decompensated liver cirrhosis (encephalopathy, gastrointestinal bleeding, impaired coagulation profile), severe renal insufficiency, sepsis and tumour burden >50% of the liver volume were not included in this analysis.

Treatment protocol

Drug Preparation for c-TACE (Transarterial Oily Based Chemoembolization):

A mixture of doxorubicin-lipiodol emulsion was used for c-TACE. The amount of lipiodol administered was between 5-15 mg and the maximum dose was 50 mg. The ratio of lipiodol to chemotherapeutic drugs in the mixture was clearly documented.

Drug Preparation for DEB-TACE:

For tumours measuring 1-5 cm, the dose administered was 50-75 mg of doxorubicin which was equivalent to 1 vial of drug eluting beads. For tumours measuring 5-10 cm, the dose given was 75-100 mg of doxorubicin, equivalent to 2 vials of drug eluting beads.

The standard approach of obtaining vascular access was via the right femoral artery and subsequently selective coeliac arteriography, right and left hepatic arteriography were obtained. A microcatheter was used for cannulation after the target feeding artery was identified to reduce vasospasm. Injection of TACE was as super-selective as possible and care was taken to prevent particle reflux to healthy liver tissue. Injection of c-TACE was at a rate of 3-4 mls/minute whilst that of DEB-TACE was at a uniform rate of 1-2 mls/minute.

Tumour response

Tumour response to the procedure was evaluated according to modified response evaluation criteria in solid tumors (mRECIST) (Brown et al., 2006; Lencioni R et al., 2010; Schultheiss et al., 2015; Vincenzi B et al., 2015). mRECIST defines treatment response into four main categories - complete response (CR), partial response (PR), progressive disease (PD), stable disease (SD). CR corresponds to disappearance of any intra-tumoral arterial enhancement in all target lesions and PR corresponds to at least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions. PD is defined as an increase of at least 20% in the sum of the diameters of viable target lesions, taking as reference the smallest sum of the diameters of viable target lesions recorded at the start of treatment and SD is defined as any cases that do not qualify for either PR or PD. Objective response rate (ORR) was defined as complete plus partial response.

Adverse effects

A complication that occurred within 4 weeks of the chemoembolization was considered a procedure-related complication. Complications monitored were bleeding, sepsis, encephalopathy and the hepatorenal syndrome. Blood tests including full blood count, serum amylase, renal profile and liver enzymes were monitored a day before and 8 hours after the procedure and daily (if needed) and appropriate treatment was given in the event of a complication arising.

Statistical analysis

Statistical analysis was performed using SPSS version 20 (IBM). Values for all continuous variables were quoted as mean, median, standard deviation, minimum and maximum range throughout. Fisher Exact Test was used to compare the differences between two categorical variables. Kaplan-Meier analysis was used to assess the primary end point which was the overall survival among patients who underwent c-TACE and DEB-TACE. The secondary end points were treatment response and treatment-related adverse events. A p value < 0.05 was considered as statistically significant.

Results

Demographic profiles and clinical characteristics of the patients

A total of 79 patients were analysed with a median follow-up of 11.8 months. Out of the 79 patients, 62 (79%) were male and 17 (21%) were female (Table 1). The age range was 21-84 years and the mean age of patients was 62 years ± 11.0 years. With regards to ethnicity, 41 (52%) were Chinese, 32 (41%) were Malay, 3 (4%) were Indian and another 3 (4%) were Somalians. With regards to CTP score, 34 (44%) patients were CTP Class A and 44 (56%) patients were CTP Class B at initial presentation.

With regards to aetiology of HCC, 27 patients (34%) had Hepatitis B (HBV), 9 (11%) had Hepatitis C and the rest were non-viral hepatitis related. According to the Barcelona Clinic Liver Cancer (BCLC) staging, 20 (25%) patients were within BCLC stage A and 59 (75%) were BCLC stage B. Twenty seven (34%) patients had a single tumour and 52 (66%) had multiple liver tumours. The mean tumour diameter was 8.02 ± 5.28 cm. Fifty two patients (66%) predominantly had right lobe disease at presentation and 27 patients (34%) presented with left lobe disease. The mean number of treatment sessions was 1.44 ± 0.82 in the c-TACE group versus 2.13 ± 1.01 in the DEB-TACE group (p=0.004). The two groups of patients either receiving c-TACE or DEB-TACE were matched with regards to baseline characteristics, tumour burden, CTP class and BCLC staging.

Treatment response

Treatment response was evaluated 3 months after TACE. At 3 months, CR was achieved in 2 (10%) *vs*. 7 (17%), PR in 4 (19%) *vs*. 9 (22%), SD in 4 (19%) *vs*. 9 (22%) and PD in 16 (52%) *vs*. 11 (39%)in the c-TACE versus DEB-TACE groups respectively. There was no statistically significant difference noted between the two groups with regards to treatment response. The objective response rates were 29% and 39% in the c-TACE and

Table 1. Demographic Profiles and Clinical C haracteristics of the Patients

Demographic	Total	c-TACE (N=34)	DCB-TACE (N=45)	p value
Mean Age, range (years)	62 ± 11, (21-84)	61 ± 10	63 ± 13	0.38
Gender				
Male	62 (79%)	26 (76.5%)	36 (80%)	0.71
Female	17 (21%)	8 (23.5%)	9 (20%)	
Race				
Chinese	41 (52%)	16 (47.1%)	25 (55.5%)	0.22
Malay	32 (41%)	13 (40.6%)	19 (42.2%)	
Indian	3 (4%)	3 (8.8%)	0 (0%)	
Others	3 (4%)	1 (2.9%)	1 (2.2%)	
Aetiology				
Hepatitis B	27 (24%)	13 (38%)	14 (31%)	0.23
Hepatitis C	9 (11%)	4 (12%)	5 (11%)	
Cryptogenic liver	18 (23%)	4 (12%)	14 (31%)	
Cirrhosis				
Liver metastases	8 (10%)	2 (6%)	6 (13%)	
Alcoholic liver	1 (1%)	1 (3%)	0 (0%)	
Cirrhosis				
Primary HCC	16 (10%)	10 (29%)	6 (13%)	
CTP Class				
A	35 (44%)	16 (47%)	19 (42%)	0.69
B	44 (56%)	18 (53%)	26 (58%)	
BCLC Staging				
A	20 (25%)	11 (32%)	9 (20%)	0.21
B	59 (75%)	23 (68%)	36 (80%)	
Total patients	79	c-TACE (N=34)	DEB-TACE (N=45)	
Mean tumour diameter (cm)	8.02 ± 5.28	8.95 ± 5.87	7.38 ± 4.81	0.22
Single lesion	27 (34%)	17 (50%)	10 (22%)	0.01
Multiple lesion	52 (66%)	17 (50%)	35 (78%)	
Primary lesion				
Left lobe	27 (34%)	11 (32%)	16 (36%)	0.77
Right lobe	52 (66%)	23 (56%)	29 (62%)	
Number of TACE				
1st	38 (49%)	24 (71%)	14 (31%)	0.004
2nd	24 (30%)	7 (21%)	17 (38%)	
3rd	9 (11%)	1 (3%)	8 (18%)	
4th	8 (10%)	2 (6%)	6 (13%)	

Table 2. Treatment-related Adverse Events in Both Groups

Complications	c-TACE (N=34)	DC Beads-TACE (N=45)	P value
Sepsis	4 (12%)	3 (7%)	0.452
Bleeding	0 (0%)	0 (0%)	NS
Hepatorenal syndrome	0 (0%)	0 (0%)	NS
Encephalopathy	0 (0%)	0 (0%)	NS

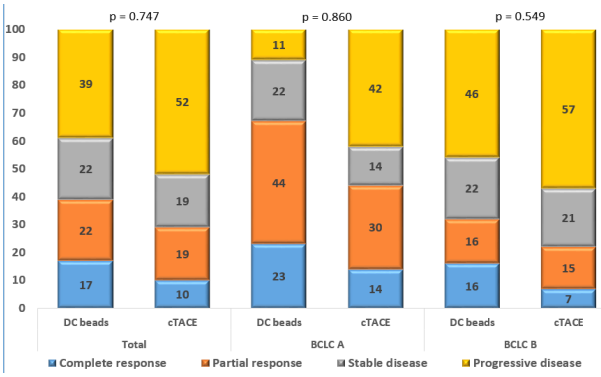

Figure 1. Treatment Response According to mRECIST in DEB-TACE and c-TACE groups. There was no significant difference in treatment response between the two groups even in patients with early and intermediate stage HCC

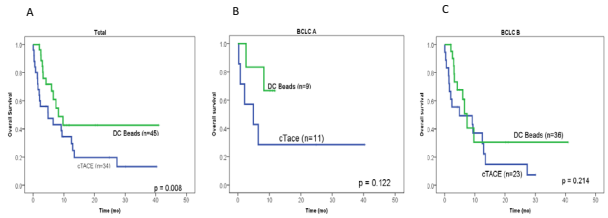

Figure 2. Overall Survival Rates in the c-TACE and DEB-TACE Groups. (A) Significantly better overall survival rates were observed in the DEB-TACE group than in the c-TACE group (p = 0.008). (B) Overall survival rates in BCLC Stage A HCC (p = 0.122). (C) Overall survival rates in BCLC Stage B HCC (p = 0.214)

DEB-TACE groups (Figure 1) respectively. Subgroup analysis of BCLC stage did not demonstrate significant difference in early and intermediate-stage HCC between the two treatment groups and neither did sub-analysis of CTP score.

Overall survival rates

The overall survival rate during the follow-up period of median 11.8 months (mean ± SD, 19.2 ± 8.0 months; range, 5.0-37.2 months) were evaluated. A total of 20 of 34 patients (80%) in the c-TACE group and 12 of 45 patients (44%) in the DEB-TACE group deceased during the follow up period. The causes of death were progression of liver disease (83.8%), cardiovascular related (10%) and pneumonia (6.2%). There were no treatment-related deaths reported. The median survival duration in the c-TACE and DEB-TACE groups was 4.9 ± 3.2 months and 8.3 ± 2.0 months respectively (p=0.008). The overall survival rates at year 1 and year 2 were 66.6% and 33% respectively. The survival rate was inferior in the c-TACE group as compared to DEB-TACE group (p=0.008) as shown in Fig 2A. Subgroup analysis however did not show significant survival difference between the two groups when compared between BCLC stage A and B respectively (Figure 2B, 2C).

Safety

There were 4 (12%) in the c-TACE and 3 (7%) patients in the DEB-TACE groups who were noted to have sepsis after the procedure. Other complications stated in Table 2 below were not observed.

Discussion

TACE has been widely used as a standard treatment for patients with unresectable HCC according to BCLC guidelines and also as a bridge to liver transplantation (Di Constanzo GG et al., 2015; Kudo M, 2015; Sasaki Y, 2015; Yang XD et al., 2015; Zu QQ et al., 2015;). The rationale for TACE is that the strong cytotoxic effect combined with ischemia as a result of superselective chemoembolization of the hepatic artery, will result in therapeutic efficacy and survival benefit when compared with supportive care (Au JS et al., 2015; Boulin M et al., 2015; Song MJ et al., 2011). The recent introduction of DEB has provided a valuable alternative to prolong the overall survival of patients with unresectable HCC (Lo et al., 2002; Llovet JM et al., 2002; Song et al., 2011). In the PRECISION V study, the use of c-TACE was associated with greater hepatic toxicity and drug related adverse effects compared to DEB-TACE (Lammer et al., 2010). However, despite the overall trend favouring treatment with DEB-TACE, a statistically significant superiority in objective response rates was observed only when focusing the analysis on subgroups of patients with more advanced disease (CTP B, ECOG 1, bilobar or recurrent disease) (Brown et al., 2006; Song et al., 2011; Lencioni et al., 2012; Ciria et al., 2015). In this study, we demonstrated a significant difference in overall survival rates between patients treated with c-TACE and those treated with DEB- TACE loaded with 50 mg doxorubicin. The difference in overall survival rates between c-TACE and DEB-TACE groups were statistically significant although subgroup analysis did not show significant differences between both treatment modalities in early and intermediate-stage HCC. In TACE studies where lobar embolisation was performed in 49% of the cases, the 1- and 2-year survival rates were reported at 57% and 31% (Lo et al., 2002). In our study, the rate was comparable at 66% and 33% respectively.

However, unlike the PRECISION V study we did not demonstrate superiority of DEB-TACE compared to c-TACE when sub-analysis of patients was done. The overall complete response (CR) and partial response (PR) were 29% and 39% in the c-TACE and DEB-TACE group respectively. These results differ from Song (2013) whereby 40% CR was achieved in the c-TACE and 60% showed a partial response. A possible explanation for this might be due to the small number of patients enrolled in

the 2013 study.

Furthermore, we demonstrated that patients undergoing DEB-TACE were significantly more likely to undergo more sessions as compared to c-TACE. This is potentially due to the fact that progressive disease (PD) was much more common in the c-TACE group. Hence, they did not remain in the BCLC stage B for long enough to undergo repeat procedures as compared to DEB-TACE.

This is the first study performed in Malaysia and the strength of this study is that it demonstrates that patients undergoing DEB-TACE have a better overall survival outcome as compared to patients undergoing c-TACE. Overall, this study strengthens the idea of using DEB-TACE as compared to the c-TACE in our multicultural Asian setting.

In conclusion, DEB-TACE appears to be a feasible, safe and promising palliative approach in the treatment of HCC when compared to c-TACE. DEB-TACE should be considered the palliative treatment of choice for patients with unresectable HCC.

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