CASE REPORT
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Transarterial chemoembolization (TACE) in hepatocellular carcinoma BCLC B patients: case series

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ABSTRACT

Introduction: Hepatocellular carcinoma (HCC) is the fifth leading cause of death for men and the seventh for women worldwide, HCC is one out of 10 most cancers in Indonesia. HCC grows in the background of chronic liver disease and often associated with hepatitis virus infection such as hepatitis B virus (HBV) and hepatitis C virus (HCV). Transarterial chemoembolization (TACE) is a minimally invasive procedure performed by interventional radiologist as the treatment of choice for intermediate stage HCC.
Case report: Here in we report a 62 and 59 years old female with hepatocellular carcinoma Barcelona clinic liver cancer (BCLC) B who were treated with TACE using 50 mg doxorubicin mixed with lopamiro and lipiodol. Both were patients with history of HBV infection. After 5 weeks of TACE, triphase abdominal CT-Scan was done to evaluate tumour progression, however one patient was loss to follow up. Evaluation of one patient was done and revealed more than 30% decrease solid viable tumour with increase of necrotic area. Expansion of necrotic area is one of the HCC treatment response criteria, while decrease tumour enhancement explains the viability of the tumour itself.
Conclusion: TACE is the therapy of choice for patient with HCC BCLC B, which can give enlargement of necrotic area and decrease tumour viability.

Keywords: Hepatocellular carcinoma, TACE, interventional radiology, CT-Scan.
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INTRODUCTION

HCC is the most common primary liver tumour accounts for 80% from all types of liver cancer, and placed the 6th as the most common liver cancer in worldwide[1], as well as listed on top ten the most common cancer in Indonesia. HCC occur more often in men than in women.[1] About 90% of HCC has background of liver disease moreover HBV and HCV infection, alcohol-related chronic liver disease and non-alcoholic steatohepatitis.[2] Other risk factors that contributes HCC occurrence are exposure of aflatoksin (such as corn, cassava, peanut, and fermented soy), diabetes mellitus, obesity, metabolic disorder or hereditary disease such as hemochromatosis.[2]

HBV is responsible for HCC incidence in about 80%. The mechanism underlying HBV-induced HCC was due to chronic necroinflammatory hepatic disease and the presence of hepatitis B e-antigen (HBeAg).[3] Malignant transformation from HBV occurs as a result of continuous or recurrent cycles of hepatocyte necrosis and regeneration causing mutagenic reactive oxygen species during the inflammatory process. HBV DNA is found in most patient who are positive for HBeAg,[3] therefore HBV DNA is the most important marker as predictor of the development of HCC in patient with HBV infection. The risk of HCC in HBV infected patients was considered if HBV DNA level is >2,000 IU/mL or equivalent to 10,000 copies/mL.[1,4]

History of HCC risk factor is important in making a diagnosis. Laboratory analysis such as alfa fetoprotein (AFP) is an important marker of HCC followed with anatomical changes observed from ultrasonography and/or abdominal CT-Scan which help in establishing HCC diagnosis.[5] Elevated AFP level more than 400-550 ng/mL is the diagnostic value of HCC,[6] however usually HCC patient has AFP value of more than 100000 ng/ml and only 30% of them has normal or low AFP value.[7]

USG helps to evaluate HCC vascularization especially to determine portal vein thrombosis and fistula. In the other hand triphase abdominal CT is the routine examination for any liver tumor. HCC is supplied by hepatic artery which explains its characteristic finding on triphase abdominal CT Scan.[7] Early wash in and rapid wash out is the pathognomonic HCC finding on triphase

abdominal CT Scan. Other characteristic including heterogenous appearance of the tumour, mosaic sign (intratumoral fibrous line), necrotic area, fat metamorphosis or calcification. Satellite nodule adjacent the primary tumour can also be found. From magnetic resonance imaging (MRI), Early wash in and wash out can also be found along with restricted diffusion area on diffusion-weighted imaging (DWI).[5,7,8] Hepatocyte-specific contrast agents such as gadoxetate acid and gadobenate dimeglumin can increase specificity and sensitivity to detect liver diseases on MRI, unfortunately its use is still limited.[8]

Barcelona clinic liver cancer (BCLC) is the staging system used for HCC to determine the therapeutical approach in every stage. Tumor size and extension, Child-Pugh liver function and physical status according to Eastern Cooperative Oncology Group (ECOG) were the criteria used to determine BCLC staging system (Table 1).

There are 5 categories of BCLC which are 0, A, B, C, and D, stated as very early stage, early, intermediate, advanced and terminal, respectively (Figure 1). Very early stage (BCLC 0) is determined by single tumour measured less than 2 cm, asymptomatic and without the presence of vascular invasion or satellite nodule. Early-stage (BCLC A) defines as patient with Child-Pugh score A/B with solitary tumour or multiple tumour (2-3) measured less than 3 cm. Multiple tumour in patient with Child-Pugh score A/B without vascular invasion or extrahepatic metastasis considered as BCLC B, while in the presence of vascular invasion or extrahepatic metastasis with physical status 1-2 belongs to BCLC C group. Terminal stage (BCLC D) has Child –Pugh score C and physical status more than 2.[10] In every stages the therapeutic approach are different, TACE is recommended as the palliative treatment on BCLC B stage.[7,9]

Table 1. Child-Pugh Score[7,9]

Factors	1 point	2 point	3 point
Bilirubin total mg/dl	<2	2-3	>3
Albumin serum g/dL	>3.5	2.8-3.5	<2.8
PT INR	< 1.7	1.71-2.30	> 2.30
Ascites	Negative	Mild	Moderate-severe
Hepatic encephalopathy	Negative	Grade I-II	Grade III-IV
	A	**B**	**C**
Total	5-6	7-9	10-15

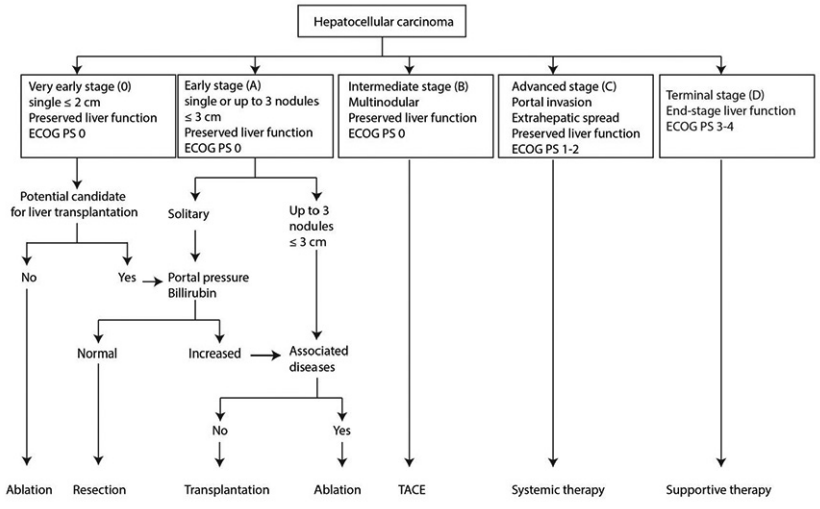

Figure 1. BCLC Staging system[10]

CASE REPORT

A 62 years old female diagnosed with HCC was referred to interventional radiologist for TACE. Upon first general examination she was conscious, slight fatigue, but still able to perform daily activities without any restriction, she felt nauseous but denied any vomiting for the past month. She experienced fullness in the upper abdomen with non-tender enlargement of the liver more than 3 cm below the right costal margin. Hematological investigation revealed slight anemic (Hb 10.57 g/dL), white blood cells 7.31 10^3 /uL, Albumin 4 g/dL, total bilirubin 2,2 mg/dL elevation of liver enzymes SGOT 139.0 u/L, SGPT 36 u/L, positive HBsAG, non reactive anti HCV, AFP 980 ng/ml, PPT 12.0 second, INR 1.13, serum creatinine 0.9 mg/dL. Abdominal CT Scan with contrast showed multiple solid tumor in the right lobe of liver measured approximately 13.6 x 14 x 19.2 cm and 4 x 3.9 x 3.7 cm which showed rapid wash in and wash out after contrast administration, without the presence of neither vascular invasion nor portal vein thrombosis (Figure 2). There was no intraabdominal fluid collection observed. From a thorough evaluation Child-Pugh score on this patient is 6 hence considered as Child-Pugh A and BCLC B was concluded, which was in tune with palliative treatment, TACE.

Another similar case, a 59 years old female with HCC, who was referred to interventional radiologist for TACE. Upon first general examination she was conscious, active and still able to perform daily activities without any restriction, she experienced vomiting and nauseous 3 months before the diagnosis however currently she denied any vomiting and nauseous. She felt fullness in the upper abdomen with non-tender enlargement of the liver more than 2 cm below the right costal margin. Hematological investigation revealed Hb 12 g/dL, white blood cells 9.01 10^3 /uL, Albumin 3.3 g/dL, total bilirubin 1,6 mg/dL elevation of liver enzymes SGOT 159.0 u/L, SGPT 40 u/L, positive HBsAG, non reactive anti HCV, AFP 1007 ng/ml, PPT 12.8 second, INR 1.16, normal serum creatinine 1 mg/dL. HCC was confirmed after triphase abdominal CT Scan with contrast showed

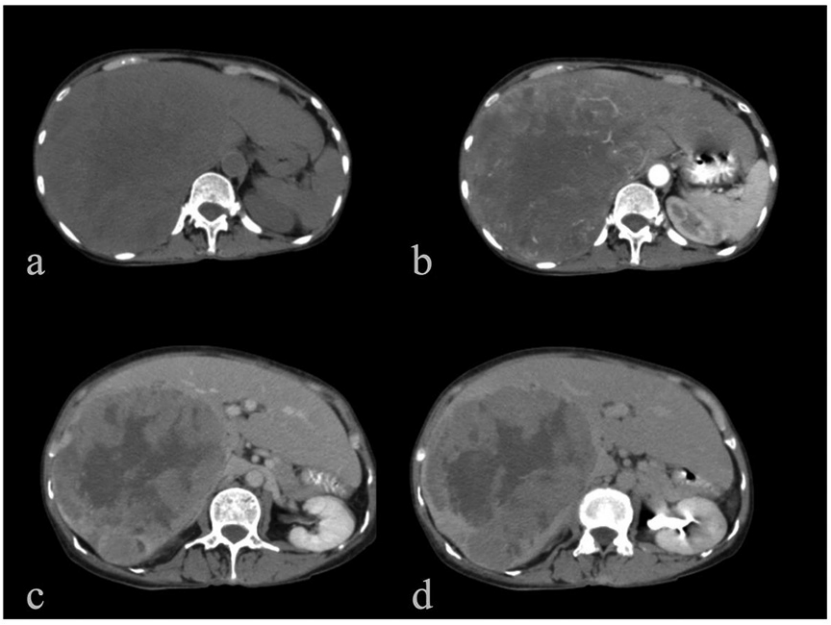

Figure 2. A 62 years old Female with HCC. A) non-contrast, B) Artery phase, C) portal phase, D) delayed phase.

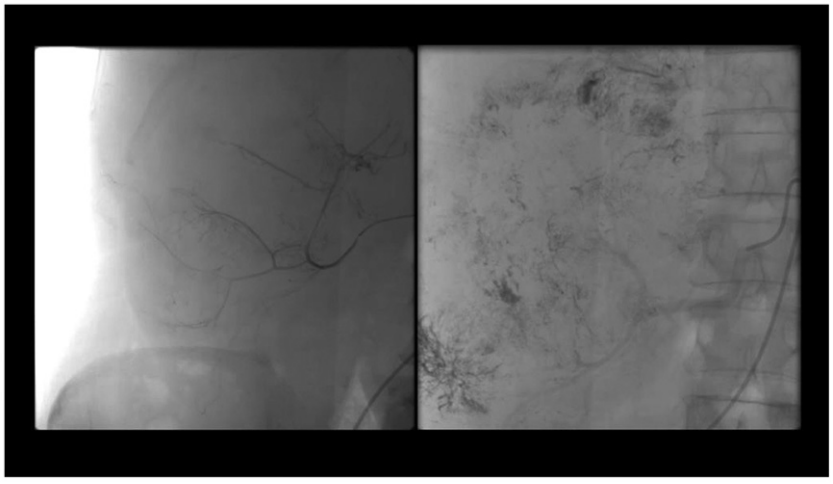

Figure 3. TACE on a 62 years old female with HCC BCLC B. Left picture showed tumor hypervascularisation, and on the right showed retention of the solution after injection.

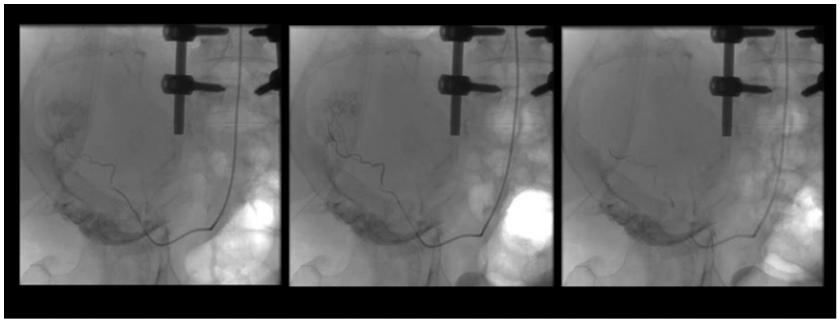

Figure 4. TACE on a 59 years old female with HCC BCLC B. Left and middle showed tumor blushing and solution retention after injection, and on the right showed minimal tumor vascularisation after all regimen had been given.

multinodular large liver tumour on the right lobe without vascular invasion or portal vein thrombosis. No ascites was observed. Child-Pugh A and BCLC B were concluded, therefore TACE was considered.

TACE was done on both patients with the same technique and regimen, using vertebral catheter 5 Fr on right femoral artery towards the aortic arch and directed to the right hepatic artery. Angiography demonstrated feeding artery from the superior, medial and inferior branches, hence mixed solution of 50 mg doxorubicin, 2 cc Iopamiro and 9.5 cc lipiodol was given in pulsatile fashion, and afterward embolization using gel foam was done (Figure 3-4).

Triphase abdominal CT-Scan was planned for both patient after 5 weeks to evaluate tumor response of treatment, however 1 patient was lost to follow up, hence only one patient can be re-evaluated. CT Scan was conducted, subsequently a before and after image was evaluated. There was increase of necrotic area from a 62 years old female patient, even though the tumor size remains relatively the same. As shown on the Figure 5, there was retention of lipiodol and lack of solid mass enhancement and tumour hypervascularity compared to the prior CT Scan before TACE procedure. Partial response according to mRECIST was concluded in this patient, due to more than 30% decrease in the sum diameter of viable tumour (Figure 6-7).

DISCUSSION

HCC is the most common primary liver tumor, and the third cause of death from cancer worldwide.[1] Locoregional therapy such as TACE, which combines chemotherapy agents and embolization, is recommended for patients with inoperable large or multifocal tumour. TACE has been proven to extend life expectancy and improve prognosis in HCC patients.[11]

Both of our presented cases belongs to Child-Pugh A class and BCLC B stage, therefore TACE was recommended as the management approach for these patient. The usual TACE done at our center is called conventional TACE, which is using chemotherapeutic regimen with lipiodol and embolant agent directly on the feeding

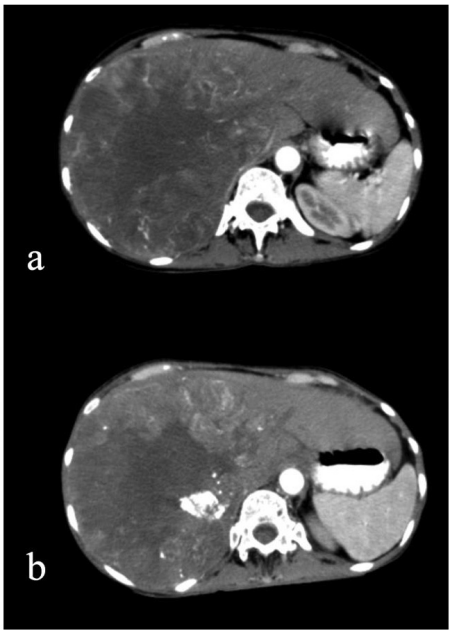

Figure 5. CT Scan of a 62 years old female with HCC BCLC B, (a) before TACE procedure, b) after, conclusion from before and after image was increased necrotic area, with decrease viable tumour, shown as decrease of tumour vascularisation and enhancement on the solid part, as well as lipiodol retention, even though the same tumor size.

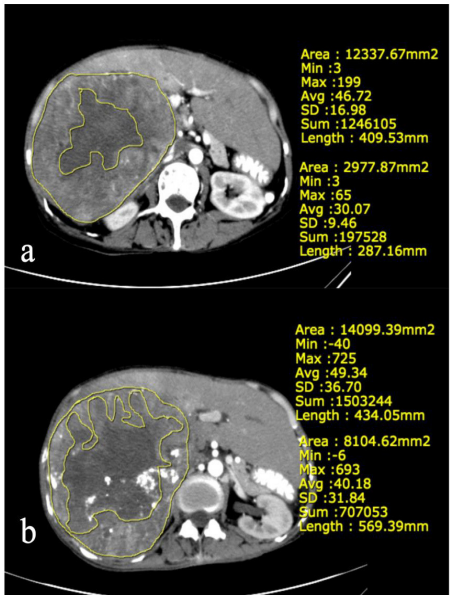

Figure 6. Solid viable tumour measurement. A) Before TACE. The thickness of the viable tumour was 9360 mm^2, B) 5 weeks after TACE. The thickness of the viable tumour was 5995 mm^2. The overall decrease tumour viability was 35%.

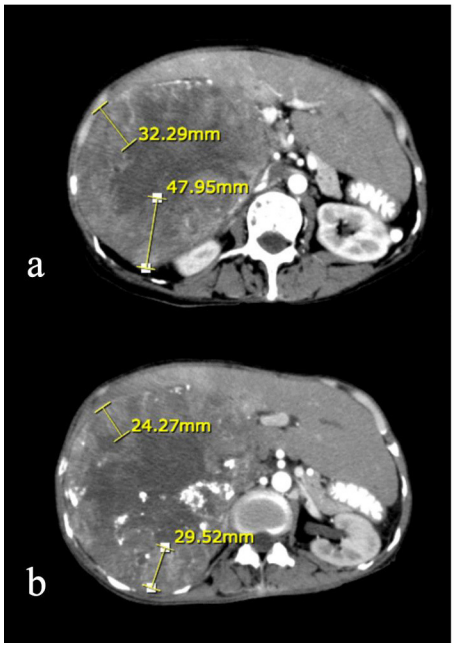

Figure 7. Diameter of viable tumor before (a) and after (b) TACE. The overall percentage was 32% decrease tumour viability.

artery of the tumour.[11] The chemotherapy drug used is usually doxorubicin 50 mg or combination of doxorubicin 50 mg and cisplatin 100 mg which diluted with water-soluble contrast, however cisplatin was not considered due to its renal toxicity.[12,13] The first patient had borderline high serum creatinine, while the second patient had slight increase serum creatinine, thus doxorubicin alone was given. The use of gel foam as a temporarily embolant agent was aimed to hold the drugs in the tumour area, creating blockage of blood flow without causing harmful total occlusion. Other than conventional TACE, currently new frontier in TACE called drug-eluting beads (DEB) TACE is increase in popularity, where the chemotherapeutic agent mixed with soluble microsphere beads that can slowly release the drug to treat the mass while the bead itself performed as an embolant agent. Several studies showed DEB TACE can reduce tumour progressivity and size, so that they can be eligible for definitive treatment such as liver transplant.[14] Unfortunately the use of DEB TACE is still limited in Indonesia.

There were no contraindications on both patients to perform TACE. Absolute contraindications for TACE are tumor resectability, persistent systemic infection, uncorrected coagulation disorder, leukopenia (WBC < 1000 u/L), cardiac or renal insufficiency (serum creatinine > 2.0 mg/dl) hepatic encephalopathy, or physical status > 2.[15,16] Relative contraindications are absence of hepatopetal blood flow, biliary obstruction with bilirubin total >3 mg/dL, lactate dehydrogenase > 425 U/I, 5 fold elevation of aspartate aminotransferase, tumor involving more than 50% of the liver, extrahepatic metastases, poor physical status, renal or cardiac insufficiency, ascites, thrombocytopenia, variceal bleeding, arteriovenous fistula, tumor invasion to inferior vena cava and right atrium, surgical portocaval anastomosis, severe portal vein thrombosis, and encephalopathy.[12]

Evaluation based on response evaluation criteria in solid tumors (RECIST) that use size as the indicator is not an optimal indicator for TACE.[14,17] Forner et al. demonstrated that RECIST missed every complete response and decrease prediction of partial response in tumour with necrosis area. Response evaluation for TACE is considered best using tumour viability instead of tumour size, hence European Association for the Study of Liver (EASL) and modified RECIST (mRECIST) give another quantification response criteria by evaluating tumour viability on enhanced CT Scan.[8,14,17] mRECIST criteria for complete response is defined as disappearance of arterial enhancement in the solid part of the tumour, while 30% decrease in the sum of diameters of viable tumour, is considered as partial response. Progressive disease is considered if there is an increase of at least 20% total diameter of viable tumor, while stable disease is referred if does not qualify for either partial or progressive response.[18] The difference between mRECIST and EASL is the percentage, EASL defines partial response as a decrease of 50% sum diameter of viable tumour, while more than 25% of tumor growth regardless of the necrosis area or there is new emerge lesion fall into progressive disease.[17,18]

Accumulation of lipiodol retention is also the biomarker for tumor necrosis, while contrast enhancement explains tumor viability. In this presented case the follow-up imaging was done on the fifth

week instead of the recommendation (after 1.5 months), to wait for all the mixture that could cause image artifact disappear,[19] however to assess response therapy after TACE using mRECIST criteria can be done after 4 weeks post TACE, thus the 5th week after TACE was considered the best time for evaluation as well as explained some of the mixture retention in the image.[20]

CONCLUSION

TACE is a locoregional therapy of choice for patient with HCC BCLC B. The use of conventional TACE showed partial response on the fifth week after therapy evaluated according mRECIST criteria, by measuring the diameter of tumor viability on arterial phase CT Scan. Several studies have showed the use of DEB TACE, a new frontier approach for HCC, gave superiority result compared to conventional TACE. Unfortunately, the use is still limited in Indonesia, therefore conventional TACE is the therapeutical approach for HCC in our center which has already showed good prognosis as in the case above.

CONFLICT OF INTEREST

The author declares there is no conflict of interest regarding publication of this article

ETHICAL CONSIDERATION

All patients had received signed informed consent regarding publication of their respective medical data in medical journal articles.

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AUTHOR CONTRIBUTION

Ni Nyoman Widiasari responsible for writing the original manuscript and case follow up. Firman Parulian Sitanggang, Putu Patriawan, and Dewa Gde Mahiswara Suadiatmika responsible for supervision and supporting to write the original draft.

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