Safety and efficacy assessment of combining chemoembolization with drug-eluting beads and conventional Tran's catheter arterial chemoembolization in patients with hepatocellular carcinoma: a single-centred experience.

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Abstract

Background and Aim: Many medical centers have applied TACE which include conventional transcatheter arterial chemoembolization (cTACE) and chemoembolization with drug-eluting beads (DEB-TACE) in their routine treatment. The dual benefit of DEB-TACE lies in their ability to enhance drug concentrations within the tumor while reducing the toxicity of the delivered payload but this procedure still has some limitations. This study reports results of combined DEB-TACE/cTACE procedure proposed by the Medical imaging & nuclear medicine center in Viet Duc hospital to improve the treatment outcome for Hepatocellular carcinoma.

Method: The sample size included 32 HCC patients. Patients were treated with DEB-TACE and then cTACE 1 month after. Multi-detector computed tomography (MDCT) scans were performed 1 month after the DEB-TACE; 1, 3 and 6 months after the cTACE. Treatment responses were measured by MRECIST and necrosis degree.

Results: Evaluating by MRECIST criteria, rate of complete response was 31.2%. The average degree of necrosis increased from 55.8% after DEB-TACE to 73.6% ($p<0.05$) after combined session (cTACE after DEB-TACE). The only side effect after 2 session of TACE was postembolization syndrome.

Conclusions: This study showed that DEB-TACE following with cTACE may be considered as a safe and effective procedure for managing large liver tumor that requiring multiple session of embolization.

Keywords: Embolization, Doxorubicin, Conventional, Hepatocarcinoma, Liver cancer.

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most common tumors worldwide with approximately 700,000 new cases are diagnosed each year throughout the world and more than 600,000 deaths are attributed to HCC each year. (1)The Barcelona Clinic Liver Cancer (BCLC) staging system integrates tumor characteristics and performance status with liver function and links them to evidence based therapeutic options.(2,3) HCC is commonly diagnosed only at intermediate (BCLC stage B) or advanced (BCLC stage C) tumor stages, when not many treatment options can be offered. (4,5)The BCLC staging system stipulates that transarterial chemoembolization (TACE) is the standard of care for patients with intermediate HCC (2). Many medical centers have applied TACE which include conventional transcatheter arterial chemoembolization (cTACE) and chemoembolization with drug-eluting beads (DEB-TACE) in their routine treatment. The dual benefit of DEB-TACE lies in their ability to enhance drug concentrations within the tumor while reducing the toxicity of the delivered payload. (3,6)

However, there are some reported issues with the performance of DEB-TACE technique. First, DEB-TACE require super-selective embolization of the tumors and after 1st procedure, the residual tumors are often fed by the small arteries or arteries extra-hepatic, such as inferior phrenic artery or branches from superior mesenteric artery, right renal artery,…*etc*. These arteries are often difficult or unable to control with microcatheter. Second, DEB-TACE has higher rate of abscess complication, the rate of abscess complication after DEB-TACE can range from 1.4% to 7.4% 2 while the rate after conventional TACE is only 0.2%.(7) To deal with the cases with peripheral enhancement on MDCT after DEB-TACE, our department propose to use cTACE after DEB-TACE to control the residual tumors and reduce risk of severe complications. This study reported the results of the combined DEB-TACE/cTACE among two groups of HCC patients (i.e, tumor less than <=50 mm, and >50 mm) in Viet Duc hospital in year 2018.

Materials and Methods

Study subjects: The sample size included 32 HCC patients. Inclusion criteria for these patients were as follow: patients who had BCLC B stage of HCC were Eastern Cooperative Oncology Group performance status, ECOG 0–1, and Child-Pugh class A (n = 31; 96.9%) and B (n = 1; 3.1%) cirrhosis. Patients with portosystemic shunts, thrombus within main portal vein, or extrahepatic metastases were excluded.

Treatment protocol: Patients were treated initially with DEB-TACE and then cTACE 1 month after. Multi-detector computed tomography (MDCT) scans were performed 1 month after the DEB-TACE; 1, 3 and 6 months after the cTACE

DEB-TACE Procedure: After hepatic and superior mesenteric artery angiography to map liver vascular anatomy, check for arteriovenous shunts, and identification of arterial tumor supply, feeding arteries were super-selectively catheterized with the use of a 2.7-Fr microcatheter (Progreat, Terumo). Slow injection of the Bead loaded with doxorubicin followed until the complete intended dose was administered or until intratumoral vascularity was obliterated and slow flow was observed. For each vial of reconstituted and loaded beads, 10 ml of contrast was used for dilution. The diameter of the beads chosen was based on the size of the lesion, the feeder/s diameter, and vascularity. In all patients, two different sizes of Bead were used: 100–300 μm and/or 300 500 μm (Biocompatibles, Terumo). Depending on the vascularity of the lesion in cases in which intratumoral flow stasis was not achieved additional embolization with Spongel followed. Each patient received 100 mg of doxorubicin loaded in one vials of Bead (2 ml total). Vigorous hydration was administered before and after embolization.

CTACE procedure: Slow injection of the mixture lipiodol doxorubicin followed until the complete intended dose was administered or until intratumoral vascularity was obliterated. Lesions supplied from extrahepatic arteries were also treated. Each patient received 50 mg of doxorubicin with 3ml -13ml lipiodol depend on residual tumors size. Vigorous hydration was administered before and after embolization.

Evaluation of safety/efficiency

MDCT evaluation: MDCT scans were performed 1 month after the DEB-TACE; 1, 3 and 6 months after the cTACE. MDCT scans were of four phases performed on a MDCT (LightSpeed VCT and Optima CT660 scanner, General Electric Medical Systems Milwaukee, WI, USA). CT parameters were: 5 mm collimation; 5-mm/sec table speed (pitch, 1.0) during a single breath-hold helical acquisition of 25 s -30 s, and a 0.625 mm reconstruction interval. The hepatic arterial, portal venous, and delayed phases were performed at 30 s, 60 s, and 180 s, respectively, after the start of the injection of 80-100 mL of nonionic iodinated contrast material, iopamidol (Iopamiro300; Bracco, Milano, Italy), *via* a peripheral vein at a rate of 4 mL/sec by power injector. Imaging measurements were made by consensus by two radiologists. Imaging evaluation for complications included search for visually detected complications including ascites, intratumoral gas collection, intraparenchymal fluid collections, cholecystitis, biliary tree dilatation pleural effusion, and pancreatic edema. Imaging response was classified according to the MRECIST (modified RECIST – The Response Evaluation Criteria in Solid Tumors)(8).

Safety evaluation: Safety was monitored by follow-up of liver enzymes at discharge (after each procedure) and synchronously with the scheduled imaging follow-up visits. Liver function tests included bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and albumin levels. Amylase levels were obtained in cases of prolonged abdominal pain (C3 days). Left ventricular function was not monitored routinely. The National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0) (9)were used to grade severity of complications. Grade 1 complications are mild, require no intervention, and include asymptomatic complications. Grade 2 events require bedside medical management and medication. Grade 3 complications are severe and require additional intervention. Grade 4 complications are those that are life-threatening and/or result in chronic disability, and a Grade 5 complication is a death related to the adverse event.

Data analysis

Data was entered in Microsoft Excel and analyzed in SPSS software version 22. Frequency table, descriptive analysis was used to present the information. Mann Whitney test was used to compare the necrosis degree between two groups. A significance level of $p<0.05$ was used

Ethical review

This study received exemption from the Scientific Research Department, Viet Duc hospital for ethical review because it was a retrospective study which based on secondary data available from Medical imaging & nuclear medicine center, Viet Duc Hospital

Results

Characteristics of participants

Table 1 presents the characteristics of 32 patients participated in the study. Most of the patients were male (90.6%). The average size of patient liver tumor was 71.4 mm (with Std=29 mm)

Table1. *Characteristics of study participants.*

Variables	
Age (mean ± SD)	57.94 ± 11.15 years
Sex Male Female	29/32 (90.6%) 3/32 (9.4%)
Etiology HBV HBV+HCV Steatosis	29/32 (90.6%) 1/32 (3.1%) 1/32 (3.1%)
Hepatic function Bilirubin serum (mean ± SD) Albumin serum (mean ± SD) Child stage A B	14.35 ± 7.13 (μmol/L) 37.8 ± 4.5 (g/L) 31/32 (96.9%) 1/32 (3.1%)
Tumor/s diameter (mean ± SD)	71.4 ± 29 mm

Measurement of Tumour shrinkage after combined DEB-TACE/CTACE:

The study used Modified Response Evaluation Criteria in Solid Tumors (i.e, MRECIST). This is a measure for treatment response, specifically to cytotoxic drugs, based on tumor shrinkage. Table 2 present the response rate after implementing DEB-TACE then cTAGE for two groups (patients with tumor size>50 mm and <= 50 mm). Rate of complete response in group 1 (tumors size >50 mm) was 22.22% (2/9), lower than this rate in groups 2 – tumors size <50 mm (34.78% - 8/23). The overall complete response for all groups was

Table 2. *Response after treatment using modified Response Evaluation Criteria in Solid Tumors (MRECIST).*

	Target lesion (%)		Overall (%)
	≤50 mm (n)	>50 mm (n)	
Complete response	2	8	10/32 (31.2%)
Partial response	4	5	9/32 (28.1%)
Stable disease	2	9	11/32 (34.4%)
Progressive disease	1	1	2/32 (6.2%)
Total	9/32	23/32	

Other outcomes after intervention

After DEB-TACE session, the average degree of necrosis among all 32 patients was 55.8% (with Std=24.5). After two combined session (cTACE after DEB-TACE), the average degree of necrosis increased significantly to 73.6% (with Std=27.0). Table 3 presents the degree of necrosis after combined DEB-TACE/cTACE by patient's tumor size. The patients with large tumor had higher degree of necrosis compared to patients with smaller tumor (74.3% vs 71.7%), however, this difference was not statistically significant. Among 32 patients, 3 patients have residual tumors that are fed from extra-hepatic artery (2 from right inferior phrenic artery and 1 from right renal artery). All 3 patients have complete response after 2 session of TACE (100% necrosis). And 1 in these 3 patients has undergone a transplantation procedure with no recurrence lesion until 6 months after the operation.

Table 3. *Degree of necrosis after TACE according to tumor size.*

	Degree of necrosis (mean ± SD %)	p*
Tumor size >50 mm (n = 23)	74.3 ± 26.9 % 71.7 ± 28.6 %	0.805
<50 mm (n = 9)		

All of patients in this series are embolized superselectively in 1st procedure with drug-eluting beads and are embolized non superselectively (with the branches origin from hepatic artery). However, no major complications (including cholecystitis, liver abscess, liver failure) were observed after TACE. The post-embolization syndrome (transient fever, abdominal pain, nausea) was the most common complication following chemoembolization; all side effects were successfully treated with medical therapy. Grading of post-embolization syndrome is shown in table 4. Mean of highest liver enzyme after the 2nd procedure AST: 197.5 ± 183.3 U/L, ALT: 119.5 ± 127.6 U/L.

Table4. *Overall incidence of per procedural complications.*

Periprocedural Complications	(% of incidents after 2 session)
Grade 1	26/32 (81.2%)
Grade 2	6/32 (18.8%)
Grade > 3	0%

Discussion

Based on MRECIST results, overall complete response of the target lesion was achieved for 10 among 32 patiens (31.2%). Otherwise, complete response for target lesion was achieved in 10/32 (31.2%). The rate of CR of the target lesion in this study was similar to that in some other trials of cTACE and DEB-TAE. Nicolini (2013) reported the rate of CR was 36.8% with DEB-TACE and 28% with cTACE.(10) Therefore, we assumed that the combined techniques that are described in this article are acceptable with the patients without potential invade to portal vein or spread into other part of the liver. The degree of necrosis in group the patients with tumor size >50 mm (34.8%) was higher than that in group with tumor size ≤50 mm, but the difference was not significant (p = 0.8). As we mentioned above, we do the embolization super-selectively in 1st procedure with DEB and non-superselectively in 2nd with lipiodol. With the larger tumor, if we embolize the tumor super-selectively with DEB, the peripheral parts of tumors that are fed from small arteries nearby will not necrotize. Therefore, the 2nd procedure with lipiodol and doxorubicin injected non-super-selectively will achieve good results.

We have 3 patients in this series have residual tumors which are fed by inferior phrenic artery and right renal artery after 1st session. After taking the angiography of these arteries we recognize that they have some anastomose and cannot be embolized with DEB. The patients have been embolized non-selectively after that and all 3 patients achieved complete response after the 2nd procedure. This combined technique may be considered as the effective solution for the similar situation. But this theory will have to be tested with larger trials to be standard technique for the tumor that are fed from extra-hepatic arteries

The only side effect after 2 session of TACE in our study was postembolization syndrome. Postembolization syndrome (PES) is a self-limited condition that is characterized by the

combination of right abdominal pain, fever fatigue, nausea, and vomiting.(11) Due to the lack of standardized criteria, PES is recorded with large differences among the different trials. Malagari et al. reported PES in all patients but no quantification of the severity is reported in any of their previous papers(12). In the study by Varela et al., it was reported in 10 of the 27 patients (37%), and it responded well to paracetamol. After the second embolization, 18% of their patients presented PES with 32% mild pain and 14% nausea and vomiting; no symptoms remained after 1 week.(13) Besides the clinical symptoms, we consider that the elevation of liver enzyme is a criteria of PES. All the patients in our study have mild PES, 6/32 patients require NSAID and response well. The cause of this condition is attributed to the extent of tumor necrosis and is considered as a positive prognostic sign of increased local response to treatment(14). In our study, in the 2nd session we do the embolization non-super selectively but use appropriate dose of lipiodol (range from 3ml to 10ml). The low toxicity rates in our study despite the fact of high rates of PES support that PES is a result of tumor necrosis rather than liver toxicity.

In conclusion, the results of this study show that DEB-TACE following with cTACE may be considered as a technique which is safe and effective technique for managing large liver tumor that require multiple session of embolization. However, we need more studies with large sample size, longer follow up time and from different countries to confirm these findings.

References

1. Surveillance Research Program, National Cancer Institute Fast stats: an interactive tool for access to SEER cancer statistics.
2. Forner A, Reig ME, de Lope CR, Bruix J. Current strategy for staging and treatment: the BCLC update and future prospects. Semin Liver Dis. 2010 Feb; 30(1):61–74.
3. Sieghart W, Hucke F, Peck-Radosavljevic M. Transarterial chemoembolization: modalities, indication, and patient selection. J Hepatol. 2015 May; 62(5):1187–95.
4. Bruix J, Sherman M, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatol Baltim Md. 2011 Mar; 53(3):1020–2.
5. European Association for the Study of the Liver, European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. 2012 Apr; 56(4):908–43.
6. Facciorusso A, Licinio R, Muscatiello N, and Di Leo A, Barone M. Transarterial chemoembolization: Evidences from the literature and applications in hepatocellular carcinoma patients. World J Hepatol. 2015 Aug 8; 7(16): 2009–19.
7. Toro A, Bertino G, Arcerito MC, Mannnino M, Ardiri A, Patane' D, et al. A Lethal Complication after Transarterial Chemoembolization with Drug-Eluting Beads for Hepatocellular Carcinoma. Case Rep Surg; 2015 Feb; 23 (1):3601-605.
8. Lencioni R, Llovet JM. Modified RECIST (MRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis. 2010 Feb; 30(1):52–60.
9. National Cancer Institute (US), Common terminology criteria for adverse events (CTCAE), Rev., NIH publication, US Dept. of Health and Human Services, National Institutes of Health, National Cancer Institute, 2009; Bethesda, Md., 194 p. In.
10. Doxorubicin-eluting bead vs. conventional transcatheter arterial chemoembolization for hepatocellular carcinoma before liver transplantation [Internet].
11. Influence of transarterial chemoembolization on angiogenesis and expression of vascular endothelial growth factor and basic fibroblast growth factor. 2019 Aug; 28 (2): 3-6
12. Malagari K, Chatzimichael K, Alexopoulou E, Kelekis A, Hall B, Dourakis S, et al. Transarterial chemoembolization of unresectable hepatocellular carcinoma with drug eluting beads: results of an open-label study of 62 patients. Cardiovasc Intervent Radiol. 2008 Apr;31(2):269–80.
13. Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics.
14. Takenaka K, Yoshida K, Nishizaki T, Korenaga D, Hiroshige K, Ikeda T, et al. Postoperative prophylactic lipiodolization reduces the intrahepatic recurrence of hepatocellular carcinoma. Am J Surg. 1995 Apr; 169(4): 400–4.

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