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Transcatheter arterial chemoembolization in recurrent unresectable hepatocellular carcinoma after orthotopic liver transplantation

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ABSTRACT

Aim: To investigate the survivals and efficacy of the doxorubicin drug eluting beads transcatheter arterial chemoembolization (TACE) in patients with recurrent hepatocellular carcinoma (HCC) status post orthotopic liver transplantation. **Methods:** Consecutive patients with HCC who underwent orthotopic liver transplantation from 2005 to 2012 were reviewed. Patients who developed recurrent HCC after orthotopic liver transplantation and received doxorubicin drug eluting beads TACE therapy were identified and included in the study. Survivals were calculated from the time of 1st doxorubicin drug eluting beads TACE of recurrent HCC. Kaplan Meier estimator with log rank test was used for survival analysis. **Results:** Eight patients had recurrent HCC after orthotopic liver transplantation and received doxorubicin drug eluting beads TACE. The overall median survival of these patients was 15.6 months. Two patients had significantly poorer overall median survival from doxorubicin drug eluting beads TACE (3.4 months) and both showed elevated serum alpha-fetoprotein levels (> 400 ng/mL) and extra-hepatic metastases (P = 0.03). Patients with poorly differentiated HCC in explant liver had the poor median overall survival (3.6 months) compared to the patients with well-to-moderately differentiated HCC (21.7 months, P = 0.004). **Conclusion:** Doxorubicin drug eluting beads TACE appears to be an effective treatment option for patients with recurrent HCC after orthotopic liver transplantation.

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the leading cause of cancer related death globally.[1] Among all the treatment options for HCC and cirrhosis, orthotopic liver transplantation (OLT) is considered the curative treatment option, especially for patients with end-stage liver disease. Unfortunately, recurrence of HCC

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occurs after OLT.[2] Many studies have reported on the patterns and prognostic factors for recurrence of HCC after liver transplantation.[3-6] However, the reported prognostic factors investigated have been focused more on histopathologic and postoperative clinical data after HCC who did not receive chemoembolization.[3-6] Several studies have been reported on the efficacy of conventional transcatheter arterial chemoembolization (cTACE) in recurrent HCC after OLT.[7,8] Little is known about the survivals, efficacy and prognostic factors following doxorubicin drug eluting beads transcatheter arterial chemoembolization (DEB TACE) in patients with recurrent HCC status post OLT.

The purposes of this study were, first, to investigate the survivals and efficacy following DEB TACE in patients with recurrent HCC status post OLT and second, to identify the prognostic factors of survivals among these patients with recurrent tumors and to report the review of the literature.

METHODS

This is a single institutional retrospective analysis of prospective database with the patient's consent, approved by the Local Institutional Review Board and is Health Insurance Portability and Accountability Act compliant.

Study objective

The primary objective of the study was to assess the survivals and efficacy following DEB TACE in patients with recurrent HCC status post OLT. And the second objective was to identify the prognostic factors of survival among these patients with recurrent HCC after OLT who were treated with DEB TACE and to report the review of the literature on the similar studies.

Patient selection

There were 420 consecutive patients with unresectable HCC who received DEB TACE therapies from December 2005 to September 2012. A total of 56 patients underwent OLT after downstaging of HCC from DEB TACE. Patients who developed recurrent HCC after OLT were identified. Those patients who underwent DEB TACE for recurrent HCC were included in the study. A total of 8 patients met the inclusion criteria and included in the study. None of the HCC tumor was feasible for surgery or ablation treatment due to size or close proximity with liver capsule or hepatic vasculature. All patients had cirrhosis before OLT. One patient was alive at the end of the study. The patients who received treatment with sorafenib were also included in the study. All patients had an initial outpatient clinical evaluation, including pertinent medical and physical evaluations. The eastern cooperative oncology group (ECOG) performance status (PS) of each patient was documented before the DEB TACE procedure. The functional liver status was determined by using the Child-Pugh criteria. The American Association for the Study of Liver Disease-Journal of the National Cancer Institute guidelines[9] were used to diagnose HCC. HCC was diagnosed if magnetic resonance imaging (MRI) showed a mass with the typical vascular pattern of arterial enhancement and portal venous "washout". For the index lesions between 1 and 2 cm, two different studies were used to detect the typical pattern and for lesions > 2 cm in diameter, only one study was used. Here, index lesion means the largest lesion in the liver. Lesions with inconclusive features on imaging were biopsied for pathologic confirmation.

DEB TACE procedure

There were 18 DEB TACE procedures performed in 8 patients. The detail techniques of the procedure were mentioned elsewhere.[10] The third or fourth order branches of feeding vessels supplying the tumor were catheterized with a 2.8 F (Renegade Hi-Flo; Boston Scientific, Natick, MA, USA) or a 2.1 F microcatheter (STC Renegade Hi-Flo; Boston Scientific, Natick, MA, USA). Then, the tumors were treated with a slow fluoroscopy-guided injection of iodinated contrast mixed 100-300 μm low compression beads impregnated with 50 mg of doxorubicin in each vial. The first and second order branches of the right or left hepatic arteries were kept patent and documented on post-embolization completion angiogram. The endpoint for treatment included the administration of the 2 vials of DEB or sluggish flow in the subsegmental branches of the hepatic artery to the region of the tumor, without an effect on the flow in the main or lobar hepatic artery. After 2 vials of DEB TACE, no additional embolization was performed despite persistent high flow within the tumor.

Follow-up

Patients with large tumors of more than 5 cm or multifocal disease were re-treated in 4 weeks and the remainders of the patients were followed up in the clinic in 4 weeks with liver function tests and an MRI of the liver. Follow-up cross-sectional imaging was performed at 4 weeks from the last single or repeat DEB TACE treatment. Further treatments were based on clinical evaluation, laboratory values, and imaging response. If there was a progressive disease on follow up MRI at 4 weeks, then the patients were assessed for systemic therapy. Simultaneously, these patients were re-treated with DEB TACE unless the disease progressed to the Barcelona-Clinic Liver Cancer D stage. If follow up MRI demonstrated residual or recurrent HCC, then the patients were retreated with DEB TACE. If patients

responded completely, then they were followed-up every 3-6 months with MRI.

Statistical analysis

Survivals were also stratified on the basis of age, gender, etiology, tumor burden, Okuda staging, ECOG PS, Child-Pugh class and Cancer of the Italian Liver Program staging. A *P*-value of 0.05 was held as significant. Survival was calculated from the time of first transcatheter therapy. The Kaplan-Meier method with the long rank test was used to estimate survival and difference. A patient was censored if he/she was alive at the end of the study period. SPSS software, version 21.0 (IBM, Somers, NY) was used to perform the statistical analyses.

RESULTS

Patient population

Eight patients had recurrence of HCC after OLT and received 18 DEB TACE treatments (range 1 to 4) after recurrence. The demographics, clinical, pathology and imaging characteristics of the patients are shown in Table 1. The mean age of the patients was 53.4 years (SD 4.6 years). The 5 patients had Child Pugh class A disease and 3 patients had Child Pugh class B disease at the time of presentation of recurrent HCC. Cirrhosis was present in all patients, diagnosed by imaging. The 7 patients had hepatitis C and 1 patient had hepatitis B. The portal venous hypertension (PHT) was present in 50% of patients. The PHT was diagnosed on MRI. Clinically, ascites was present in 1 patient. The mean size of the index tumor was 3.3 cm (SD 0.85 cm). Portal vein thrombosis or invasion was not present in any of the patients and extra-hepatic metastases were present in 25% of the patients (*n* = 2) at the time of initial presentation. The 1 patient has T11 vertebral body metastasis and showed mildly increased activity on computed tomography (CT) positron emission tomography examination. The other patient had a single 9 mm lung metastasis on CT chest and it was surgically resected. These both patients had alpha-fetoprotein (AFP) of greater than 2,400 ng/dL. During DEB TACE therapies, 25% (*n* = 2) of patients received concurrent sorafenib systemic chemotherapy. The 6 patients (75%) had solitary HCC and unilobar involvement after OLT. The 30-day mortality was zero.

Survival analysis

The overall median and mean survivals from the time of 1st DEB TACE were 15.6 and 19.6 months accordingly. The mean recurrence free survival from the time of OLT was 50.5 months. The mean survival from the time of the OLT was 72.1 months. One year and 2-year survivals from the time of 1st DEB TACE were 62.5% (5/8) and 50% (4/8) respectively. The univariate survival analyses were performed for different categories as shown in Table 2. Two patients had significantly poor overall survivals from DEB TACE (3.27 and 3.4 months) as compared to other patients and both showed elevated serum AFP levels (> 2,400 ng/mL) and extra-hepatic metastases [Table 2]. The

Table 1: Demographics, clinical, imaging, staging and survival characteristics of recurrent HCC patients after OLT treated with DEB TACE

Variables	P 1	P 2	P 3	P 4	P 5	P 6	P 7	P 8
Age (years)	51.7	44.5	54.0	59.5	55.0	51.4	52.7	58.3
Living status	Alive	Dead	Dead	Dead	Dead	Dead	Dead	Dead
Gender	Male	Male	Male	Male	Male	Male	Female	Female
Race	White	Other	White	White	White	Black	White	Other
Etiology	Hepatitis C	Hepatitis B	Hepatitis C	Hepatitis C	Hepatitis C	Hepatitis C	Hepatitis C	Hepatitis C
Index tumor size (cm)	2.2	2.2	2.8	3.1	3.3	3.9	4.1	4.7
Number of the tumor	1	12	1	9	1	1	1	1
Histology grading of the explant liver HCC	Well or moderately differentiated	Poorly differentiated	Poorly differentiated	Well or moderately differentiated	Well or moderately differentiated	Well or moderately differentiated	Well or moderately differentiated	Well or moderately differentiated
Metastases at time of recurrent HCC presentation before DEB TACE	No	Yes	No	No	No	Yes	No	No
Alfa-fetoprotein (ng/dL) of recurrent HCC	5	>2,400	<5	10.6	11.8	>2,400	40.9	9.8
Child-Pugh class of recurrent HCC	A	B	A	A	B	A	A	B
Tumor free survivals from OLT (months)	32.9	25	13.7	83.1	117	40.3	28.4	63.6
Concurrent sorafenib treatment	No	Yes	No	No	No	Yes	No	No

P: patient number; DEB TACE: doxorubicin drug eluting beads transcatheter arterial chemoembolization; OLT: orthotopic liver transplantation; HCC: hepatocellular carcinoma

shortest survival from DEB TACE was 3.4 months and the patient had hepatitis B and more than 12 HCC tumors with extra-hepatic metastasis and AFP > 2,400 ng/mL. Survival curves generated by Kaplan Meier analysis according to the status of AFP and metastases are shown in the Figure 1A and B. The histology grading of HCCs of the explant liver was correlated with the survivals. The patients with poorly differentiated HCC had the poor overall survivals (3.4 months) compared

Table 2: Median survivals (from 1st DEB TACE) HCC patients after OLT treated with DEB TACE

Demographics	Number of patients	Median survival (months)	*P* value
Total number of patients	8	15.6	
Child-Pugh class			
A	5	21.7	0.45
B	3	15.6	
Okuda staging			
I	6	9.3	0.9
II	2	15.6	
CLIP staging			
Early	3	39.4	
Intermediate	5	15.6	0.2
ECOG performance status			
0	4	39.4	
1	3	21.7	0.3
2	1	7.7	
Imaging findings			
Ascites			
Present	1	26.8	0.7
Absent	7	15.6	
Portal hypertension			
Present	4	7.8	0.2
Absent	4	21.7	
Tumor morphology			
Tumor locations			
Unilobar	6	15.6	0.27
Bilobar	2	3.4	
Number of tumors			
Solitary	6	15.6	0.14
Multiple	2	3.4	
Size of index tumor			
< 3 cm	6	15.6	
3 cm or more	2	7.8	0.87
Extrahepatic metastasis			
Present	2	3.4	0.03
Absent	6	21.7	
Laboratory data			
Serum alpha-fetoprotein level (ng/dL) of recurrent HCC			
< 400	6	21.7	0.03
≥ 400	2	3.4	
Histology grading of the explant liver HCC			
Well or moderately differentiated	6	21.7	0.004
Poorly differentiated	2	3.6	

HCC: hepatocellular carcinoma; DEB TACE: doxorubicin drug eluting beads transcatheter arterial chemoembolization; OLT: orthotopic liver transplantation; CLIP: Cancer of the Italian Liver Program; ECOG: eastern cooperative oncology group

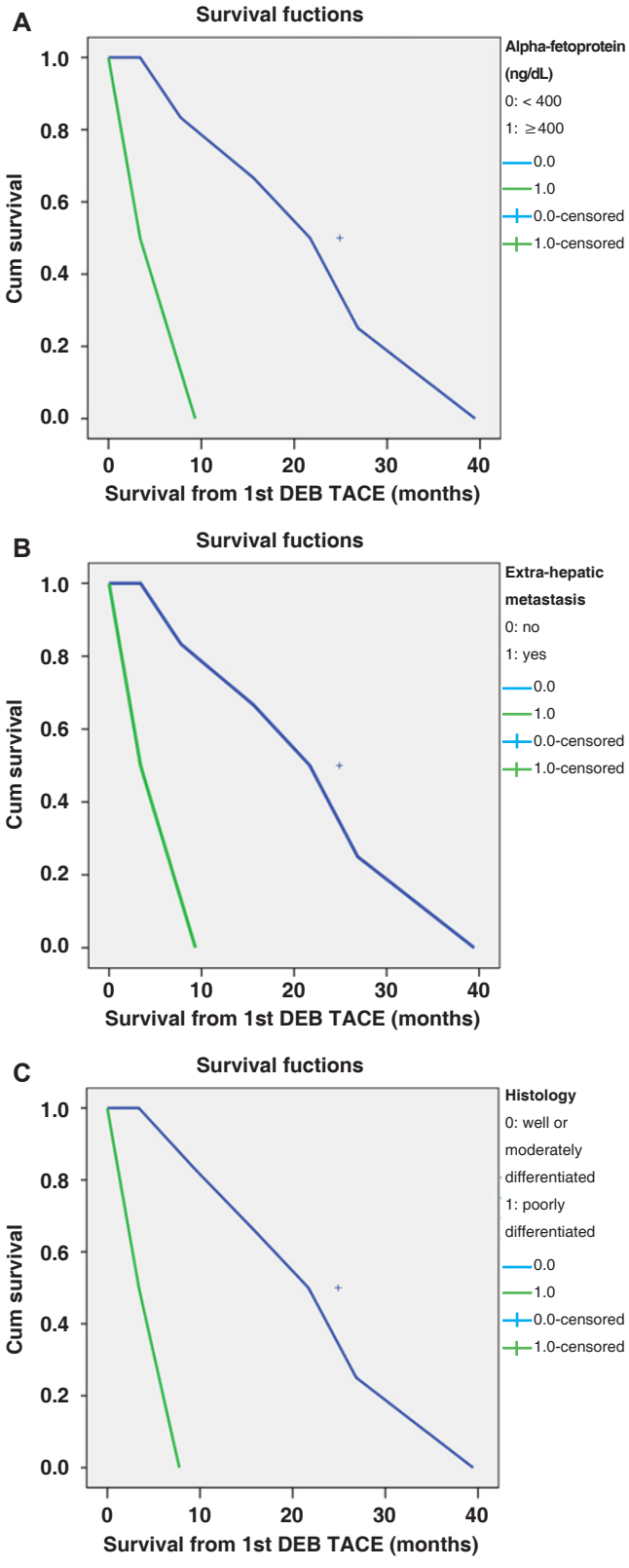

Figure 1: Survival curves generated by Kaplan Meier analysis according to the status of alpha-fetoprotein level (A), presence or absence of the extra-hepatic metastasis (B) and histology grading of the explant liver (C) before DEB TACE in patient with recurrent HCC after orthotopic liver transplantation. HCC: hepatocellular carcinoma; DEB TACE: doxorubicin drug eluting beads transcatheter arterial chemoembolization

to the patients with well or moderately differentiated HCC of the explant liver (21.7 months, $P = 0.004$). The survival curve generated by Kaplan Meier analysis according to the status of histology grading of the explant liver is shown in the Figure 1C. Although, there was a survival difference in the patients between Child A and B disease, statistically it was found nonsignificant. This can likely be due to small sample size. In this study, 25% patients received concurrent treatment with sorafenib with a median survival of 7.7 months compared to a median survival of 21.7 months in patients who did not receive sorafenib ($P = 0.19$).

DISCUSSION

Recurrence of HCC after liver transplantation has a major effect on reducing patient's overall survival.[11] In general, all treatment options currently available for advanced HCC are also potentially feasible after OLT. Treatments include resection, ablation, transarterial embolization or radioembolization, and systemic treatment with sorafenib. The 5-year posttransplant survival was 47% for patients who underwent surgical resection to treat recurrence.[11] The ability for surgical treatment and a late onset (> 24 months) of recurrence are factors associated with long-term survival.[12] Local ablative techniques, such as radiofrequency ablation, cryoablation, or percutaneous ethanol ablation, also yield favorable survival outcomes in patients with small unresectable recurrent HCC.[13,14] In our study, none of the HCC tumor was feasible for surgery or ablation treatment due to size or close proximity with liver capsule or hepatic vasculature. All patients had cirrhosis before OLT. In 2007, sorafenib was the first agent to demonstrate a significant improvement in the overall survival of patients with advanced HCC.[15,16] The survival benefits from sorafenib ranged from 2 to 3 months in advanced HCC patients.[15,16] Since these two landmark studies, saorafenib has become the standard of care for advanced HCC patients. It has also shown improved survival benefits in patients with recurrent HCC after OLT as compared to best supportive care.[17] Yittrium-90 radioembolization has shown benefits in HCC patients.[18] However, no specific radioembolization study was found in patients with recurrence of HCC after OLT.

DEB TACE is a well-known locoregional treatment for HCC evaluated by multiple randomized controlled studies. Recently, numerous studies have been reported favorable outcomes with the use of DEB TACE for HCC.[10,19-22] DEB TACE has demonstrated improved survival, better tolerability, and fewer side effects as compared to conventional TACE.[19,21-23] In these reported DEB TACE studies, the survivals in patients with unresectable HCC, ranged from 13.5 to 24.5 months.[10,19-22] In the current study, the overall median and mean survivals from the time of 1st DEB TACE were 15.6 and 19.6 months accordingly, which is comparable with the reported DEB TACE studies.

Little is known on the survivals, efficacy and prognostic factors of survivals following DEB TACE in patients with recurrent HCC status post OLT. Few similar studies were found from English literature.[7,8] Zhou *et al*.[7] reported that conventional TACE is safe following in patients with recurrent HCC status post OLT. Their study indicated that TACE treatment seems to produce an effective tumor response for targeted recurrent HCC after liver transplantation. The Child Pugh Class of HCC patient is considered to be the one of the main prognostic factors for survival following TACE in HCC patients.[24-26] In our study, there was a survival difference in the patients between Child A and B disease. However, statistically it was found nonsignificant. This can likely be due to small sample size.

Recurrence of HCC ranged from 10% to as high as 40%.[2,27,28] Therefore, surveillance with MRI of the abdomen is very important in these patients. Patients with early recurrence had much worse overall survival than those with late recurrence.[2,27,28] In our studies, 2 patients had shortest tumor free survival of 13.3 and 25 months and had worst overall median survivals of 3.4 and 7.7 months respectively. Both patients had poorly differentiated HCC of the explant liver. The patients with poorly differentiated HCC had the poor overall survivals (3.4 months) compared to the patients with well to moderately differentiated HCC of the explant liver (21.7 months, $P = 0.004$). A histological grade of HCC is an important prognostic factor affecting patient survival after OLT. The importance of the grade of the histology of the explant liver HCC in patient's prognosis has previously reported.[5,6,29]

The prognostic factors for poor survivals other than the histology grading, the number and size of the tumors have been reported by many investigators. These factors include microscopic vascular invasion by the HCC,[30,31] presence of partial necrosis of the nodule in the explanted specimen,[32] presence of microscopic satellite nodules in the explanted specimen,[33] specific type of lymphocytic infiltrate to the tumor as immune response,[34] high preoperative level of serum AFP,[35] and advanced tumour-node-metastasis stage and extra-hepatic metastases.[4,5] In this study, 2 patients had elevated AFP and extra-hepatic metastases had the poorest survivals. As these facts help in identifying the patients who will get the most benefit from the DEB TACE treatment.

We acknowledge, this study has several limitations. First, the sample size of the study is small and so results should be taken as preliminary data. Second, this is a single institution non-randomized study, so selection bias and late look bias may be inherent. Third, patients who were treated with sorafenib (25%) were also included in this study, so outcomes after DEB TACE may be confounded. However, concomitant therapy with sorafenib did not significantly affect survival in univariate analysis. Therefore, we believe that survival advantage in this study is largely from the effect of DEB TACE therapy.

In conclusion, recurrence of HCC after OLT is not uncommon. DEB TACE could help to extend the survival of the patients with recurrent HCC after OLT. As the sample size of the study is small, the results should be taken as preliminary. Further, multi-institutional prospective trial is needed to explore its benefit on these patients with recurrence of HCC after OLT. Patients with poorly differentiated HCC of explant liver, > 400 ng/dL AFP and metastases at the time of TACE had a poor overall prognosis.

DECLARATIONS

Authors' contributions

All three authors were involved with study concept, design, acquisition of data, analysis and interpretation of data, drafting of the manuscript and critical revision of the manuscript for important intellectual content.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

Patient consent

Obtained.

Ethics approval

The study is approved by the Local Institutional Review Board and is Health Insurance Portability and Accountability Act compliant.

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