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ORIGINAL ARTICLE

Prognostic factors for survival in patients with unresectable hepatocellular carcinoma undergoing chemoembolization with doxorubicin drug-eluting beads: a preliminary study

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Abstract

Background: Transarterial chemoembolization (TACE) with drug-eluting beads (DEB) is a new treatment modality. Little is known about prognostic factors affecting survival after DEB TACE for patients with hepatocellular carcinoma (HCC).

Methods: Patients who underwent TACE with doxorubicin DEB for unresectable HCC during 2006–2008 were studied. Survival was calculated from the day of first transcatheter therapy. Survival analysis was performed using Kaplan–Meier estimations. Survival curves were compared using the log-rank test.

Results: Fifty patients underwent chemoembolization with doxorubicin DEB. They included 39 women and 11 men, with a median age of 57.5 years (range 28–91 years). Eighteen patients died during the study period and 32 remained alive. Overall survival rates at 6 months, 1 year and 2 years from the first administration of doxorubicin DEB TACE were 71%, 65% and 51%, respectively. Prognostic factors found to be significant on univariate analysis were Child–Pugh class, Okuda staging, bilirubin > 2 mg/dl, albumin < 3.0 g/dl, Model for End-stage Liver Disease (MELD) score, serum alphafetoprotein (AFP), Cancer of the Liver Italian Programme (CLIP) score, tumour satisfying Milan criteria, Eastern Cooperative Oncology Group (ECOG) performance status (PS) and Barcelona Clinic Liver Cancer (BCLC) staging.

Conclusions: Child–Pugh class, Okuda staging, bilirubin > 2 mg/dl, albumin < 3 g/dl, MELD score, serum AFP, CLIP score, Milan criteria, ECOG PS and BCLC staging were found to be prognostic markers of survival after treatment with doxorubicin DEB TACE in patients with unresectable HCC.

Keywords

hepatocellular carcinoma, chemoembolization, prognosis, drug-eluting beads

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Introduction

Hepatocellular carcinoma (HCC) is a lethal malignancy, the incidence of which has continually increased in the USA over the past two decades.[1] Transplantation and resection are curative therapies for HCC. The majority of patients, however, are not eligible for surgery because of advanced tumour, multifocal disease or poor liver reserve.[2] Conventional transarterial chemoembolization (TACE) has been used as palliative treatment for patients with HCC who are ineligible for resection or transplantation. The survival benefit of this treatment over supportive care has been shown by two prospective randomized controlled trials carried out in 2002 in patients with unresectable HCC.[3,4]

Drug-eluting beads (DEB), which can be loaded with doxorubicin, represent a novel drug delivery system for chemoembolization. A slow and sustained release of drug is expected after intra-arterial delivery of DEB. Clinical studies by Varela *et al.*[5] and Malagari *et al.*[6] have reported this new drug delivery method to be safe and efficacious in the treatment of HCC. DEB TACE has been proposed to have a better pharmacokinetic profile than

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conventional TACE and to result in decreased systemic adverse effects.[7]

Factors which predispose patients to develop hepatic failure and related complications after transarterial treatment are generally identified as exclusion criteria during patient selection. Large tumours, poor liver reserve and portal vein thrombosis (PVT) have been associated with poorer outcomes in patients treated with conventional chemoembolization.[8–10] Because DEB TACE is a new treatment modality, little is known about prognostic factors affecting survival after DEB TACE in patients with HCC. The aim of this study was to identify prognostic factors which influence survival from the time of transcatheter therapy in patients with unresectable HCC treated with doxorubicin DEB chemoembolization.

Materials and methods

Patient selection

The study was approved by the local institutional review board. Consecutive patients with HCC who underwent chemoembolization with doxorubicin DEB at a single institution during a period of 3 years (January 2006 to December 2008) were reviewed. A prospective database for patients treated after July 2008 was used, and data were collected retrospectively from case records for patients treated between January 2006 and June 2008. Patients were excluded if they had: (i) undergone resection; (ii) undergone radiofrequency ablation; (iii) received conventional chemoembolization, bland embolization or radioembolization with yttrium 90 (Y-90); (iv) received therapy with more than one type of embolic agent, or (v) received systemic chemotherapy such as sorafenib (Nexavar; Bayer Corp., Pittsburgh, PA, USA).

The American Association for the Study of Liver Diseases (AASLD) guidelines[11] were used to diagnose HCC. This diagnosis was made if dynamic computed tomography (CT) or magnetic resonance imaging (MRI) showed a mass with typical vascular pattern, arterial enhancement and portal venous 'washout'. For lesions sized 1–2 cm, two different studies were used to detect a typical pattern; for nodules >2 cm in diameter, only one typical study was used. Lesions with doubtful or inconclusive features on imaging were biopsied.

Okuda staging, Cancer of the Liver Italian Programme (CLIP) score and the Barcelona Clinic Liver Cancer (BCLC) staging system (Tables 1–3) have been used to stage HCC.[12–14] The Eastern Cooperative Oncology Group (ECOG) system has been used to grade performance status (PS).[15]

Data collection

Demographic (age, gender, ethnicity), clinical (aetiology, complications), laboratory parameters (bilirubin, albumin, creatinine, international normalized ratio [INR], alphafetoprotein [AFP]) and imaging (number of lesions, distribution, size, PVT) data were collected from patient case records. All patients underwent CT or MRI within 1 month before the procedure to assess tumour

Table 1 Okuda staging

	0 points	1 point
Tumour size	<50% of liver	>50% of liver
Ascites	No	Yes
Albumin	>3.0 g/dl	<3.0 g/dl
Bilirubin	<3.0 mg/dl	>3.0 mg/dl

Stage I = 0 points; Stage II = 1,2 points; Stage III = 3,4 points

Table 2 Cancer of the Italian Liver Programme (CLIP) staging

	0 points	1 point	2 points
Child–Pugh class	A	B	C
Alphafetoprotein	<400	≥400	
Portal vein thrombosis	Absent	Present	
Tumour	Single, <50%	Multiple, <50%	Multiple, >50%

Early stage = 0 points; intermediate stage = 1–3 points; advanced stage = 4–6 points

Table 3 Barcelona Clinic Liver Cancer (BCLC) staging

	Performance status	Tumour stage	Okuda stage	Liver function
Stage A				
A1	0	Single < 5 cm	I	No portal hypertension
A2	0	Single < 5 cm	I	Portal hypertension, normal bilirubin
A3	0	Single < 5 cm	I	Portal hypertension, elevated bilirubin
A4	0	Up to 3, <3 cm	I–II	Child–Pugh class A–B
Stage B	0	Large multi-nodular	I–II	A–B
Stage C	1–2	Vascular invasion or extrahepatic disease	I–II	A–B
Stage D	3–4	Any	III	C

burden and presence of PVT. Hepatocellular carcinoma with more than five discrete nodules was referred to as diffuse tumour. Mean tumour size was calculated by the sum of the longest diameter of all measurable tumours.

Procedure

The type of therapy patients received was determined in a multidisciplinary liver tumour conference. Transcatheter therapy was performed via femoral artery approach under moderate sedation. Coeliac and superior mesenteric arteriograms were obtained to assess the arterial anatomy of the liver, tumour vasculature and portal vein patency. The chemotherapeutic agents were infused into the hepatic artery supplying the tumour(s). Patients who underwent chemoembolization with doxorubicin DEB received 300–500 μm and 500–700 μm LC beads (Biocompatibles PLC, Farnham, UK) impregnated with 75 mg of doxorubicin in each vial, or 100–300 μm LC beads impregnated with 50 mg of doxorubicin in each vial. Subsegmental or segmental chemoembolization were performed whenever possible. Flow in main and branch arteries supplying tumours were kept patent to maintain access for potential subsequent interventions. All patients were kept under observation for a period of 24 h and analgesia was administered as necessary.

Follow-up

Follow-up cross-sectional imaging (contrast-enhanced CT or MRI) was performed 3–4 weeks after treatment. Further treatments were based on clinical evaluation, laboratory values and imaging response. Patients with progressive disease underwent repeat treatments with the same modality. Patients with stable disease were followed with cross-sectional imaging every 3 months.

Statistics

Survival time is defined as the time from the first doxorubicin DEB chemoembolization to the date of death. Survival analysis was performed using Kaplan–Meier estimation. In univariate analysis, survival estimates were compared with log-rank test in the Kaplan–Meier method. Multivariate analysis was not carried out as the small sample size and low number of events per variable in the study could potentially lead to inconclusive results. SPSS Graduate Version 16.0 (SPSS, Inc., Chicago, IL, USA) was used for all statistical computations.

Results

A total of 50 patients with HCC who underwent chemoembolization with doxorubicin DEB and satisfied the inclusion criteria were included in the study. They included 39 women and 11 men, with a median age of 57.5 years (range 28–91 years). Eighteen patients (36%) died during the study period. Demographic, clinical, laboratory, tumour staging and imaging characteristics are summarized in Table 4.

The median duration of follow-up was 359 days (range 33–984 days). Median survival could not be calculated because more than 50% of the patients were alive at the end of the study period. Overall survival rates at 6 months, 1 year and 2 years from the first administration of doxorubicin DEB were 71%, 65% and 51%, respectively.

Univariate analysis

Univariate analyses of patient- and tumour-related variables along with various prognostic scoring systems are given in Table 5. Prognostic factors found to be associated with survival on univariate analysis were Child–Pugh classes A and B, early Okuda stage, bilirubin < 2.0 mg/dl, albumin > 3.0 g/dl, low Model for End-stage Liver Disease (MELD) score, AFP < 400 ng/ml, CLIP score < 3, tumour within the Milan criteria, ECOG PS of 0 and early-intermediate BCLC stages. Age, gender, ethnicity, PVT, creatinine, INR and tumour size were not found to be significant prognostic factors.

Discussion

Chemoembolization with doxorubicin DEB is a novel drug delivery system which performs the dual function of vascular embolization and intra-tumour drug delivery. Studies by Varela *et al.* and Malagari *et al.* demonstrate that chemoembolization is an effective procedure with a favourable pharmacokinetic profile.[5,6] Identifying the subset of patients with unresectable HCC, in whom doxorubicin DEB TACE can prolong survival, is critical to improving clinical outcome.

Univariate analysis in this study showed Child–Pugh class, Okuda staging, bilirubin > 2 mg/dl, albumin < 3.0 g/dl, MELD score, serum AFP, CLIP score, Milan criteria, ECOG PS and BCLC staging to be significant prognostic factors for survival. Most of the earlier studies investigating prognostic factors for transcatheter therapies have focused on conventional chemoembolization. Table 6 summarizes the various prognostic factors for survival in patients with unresectable HCC in some of the published studies.[8,9,16–21] Child–Pugh score and tumour size and stage have been found to be significant predictors of survival after conventional chemoembolization in most studies.[8,9,17] The results of the current study are comparable with those of conventional chemoembolization as both Child–Pugh score and tumour stage (as assessed by Okuda and BCLC staging) were found to be prognostic factors in this study. However, tumour size and PVT, which were among the prognostic factors for conventional chemoembolization, were not found to influence survival after treatment with DEB in the present study.

Advanced tumour stage (tumour burden > 50% of liver), infiltrative type of tumour, poor liver function (bilirubin > 2.0 mg/dl; albumin < 3.0 g/dl; elevated AST/ALT), and presence of PVT were found to be prognostic factors for survival after treatment with Y-90 radioembolization.[20,21] In the current study, elevated bilirubin and elevated AFP were found to be prognostic factors on

Table 4 Demographic and clinical characteristics

Patient characteristics	Category	*n* (%)
Age at diagnosis, years	Median (range)	57.50 (28–91)
Gender	Male	39 (78.0%)
	Female	11 (22.0%)
Ethnicity	White	37 (74.0%)
	African-American	6 (12.0%)
	Other	7 (14.0%)
Aetiology	HCV	24 (48.0%)
	HBV	6 (12.0%)
	ALD	7 (14.0%)
	Cryptogenic	7 (14.0%)
	Others	6 (12.0%)
Child–Pugh class	A	24 (48.0%)
	B	14 (28.0%)
	C	12 (24.0%)
MELD score	Median (range)	11.0 (7–28)
Tumour characteristics	Uni-nodular	26 (52.0%)
	Multi-nodular (2–5 nodules)	15 (30.0%)
	Diffuse (>5 nodules)	9 (18.0%)
	Mean tumour size	5.49 cm (1.0–20.7 cm)
	Portal vein thrombosis	12 (24.0%)
	Satisfying Milan criteria	31 (62.0%)
Bilirubin, mg/dl	Median (range)	1.6 (0.4–10.7)
Albumin, g/dl	Median (range)	2.8 (1.8–5.0)
INR	Median (range)	1.2 (0.9–1.9)
Creatinine, mg/dl	Median (range)	1.0 (0.2–9.8)
AFP, ng/l	Median (range)	43.7 (5–2400)
AFP	<400 ng/l	43 (86.0%)
	>400 ng/l	7 (14.0%)
ECOG PS	0	33 (66.0%)
	1	15 (30.0%)
	2	2 (4.0%)
BCLC staging	Stage A	
	A1	0 (0.0%)
	A2	7 (14.0%)
	A3	6 (12.0%)
	A4	2 (4.0%)
	Stage B	9 (18.0%)
	Stage C	8 (16.0%)
	Stage D	18 (36.0%)
CLIP staging		
	0	7 (14.0%)
	1	12 (24.0%)
	2	10 (20.0%)
	3	10 (20.0%)
	4–6	11 (22.0%)
Okuda staging		
	I	24 (48.0%)
	II	14 (28.0%)
	III	12 (24.0%)

HCV, hepatitis C virus; HBV, hepatitis B virus; ALD, alcoholic liver disease; MELD, Model of End-stage Liver Disease; INR, international normalized ratio; AFP, alphafetoprotein; ECOG, Eastern Cooperative Oncology Group; PS, performance status; BCLC, Barcelona Clinic Liver Cancer; CLIP, Cancer of the Liver Italian Programme

Table 5 Univariate analysis of prognostic factors

Variable	Category	*n* (events)	1 year	2 years	HR (95% CI)	*P*-value
Age at diagnosis	<60 years	27 (10)	77%	61%	1.1 (0.4–3.6)	0.819
	>60 years	23 (8)	74%	55%		
Gender	Male	39 (12)	64%	52%	1.3 (0.7–2.3)	0.291
	Female	11 (6)	72%	64%		
Ethnicity	White	37 (13)	71%	62%	0.6 (0.2–2.1)	0.372
	Non-White	13 (5)	83%	63%		
Child–Pugh class	A	24 (6)	82%	73%	6.1 (1.7–22.3)	0.002
	B	14 (4)	75%	58%	1.3 (0.3–5.5)	
	C	12 (8)	50%	0%		
MELD score	<15	36 (10)	75%	67%	1.1 (0.9–1.2)	0.01
	>16	14 (8)	57%	29%		
Okuda stage	I	24 (3)	90%	67%	6.6 (1.4–30.6)	0.005
	II	14 (9)	67%	24%	5.2 (0.9–29.2)	
	III	12 (6)	48%	0%		
AFP	<400 ng/l	43 (8)	81%	74%	3.9 (1.4–11.2)	0.005
	>400 ng/l	7 (10)	29%	14%		
Portal vein	Thrombosed	12 (5)	58%	40%	0.4 (0.1–1.1)	0.128
	Patent	38 (13)	73%	64%		
Bilirubin	<2 mg/dl	32 (9)	81%	73%	2.8 (1.0–7.8)	0.038
	>2 mg/dl	18 (9)	50%	25%		
Albumin	>3.0 g/dl	19 (4)	88%	67%	5.3 (1.1–23.6)	0.015
	<3.0 g/dl	31 (14)	46%	35%		
Tumour burden	Uni-nodular	26 (8)	70%	62%	1.3 (0.7–2.6)	0.100
	Multi-nodular	15 (4)	73%	48%	1.1 (0.6–2.1)	
	Diffuse	9 (6)	44%	0%		
Milan criteria	Within	31 (10)	76%	58%	0.35 (0.1–0.9)	0.038
	Beyond	19 (8)	47%	31%		
CLIP score	<3	29 (5)	89%	70%	7.3 (2.0–25.0)	<0.001
	≥3	21 (13)	35%	23%		
BCLC stage	Early-intermediate	32 (8)	73%	62%	3.9 (1.3–11.6)	0.009
	Advanced	18 (10)	28%	0%		
ECOG PS	0	33 (5)	82%	82%	4.1 (2.0–8.3)	<0.001
	1–2	17 (13)	35%	12%		

HR, hazard ratio; 95% CI, 95% confidence interval; MELD, Model of End-stage Liver Disease; AFP, alphafetoprotein; CLIP, Cancer of the Liver Italian Programme; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; PS, performance status

univariate analysis. The BCLC staging takes serum AFP, bilirubin levels and PS into consideration, and BCLC stage was found to be a prognostic factor in this study. Several studies have shown that Child–Pugh classification is one of the most powerful predictors of survival after transarterial chemoembolization.[9,17,18,22] Georgiades *et al.* compared the prognostic accuracy of 12 HCC tumour staging systems and found the Child–Pugh scoring system to be the most accurate for predicting survival after conventional chemoembolization.[23] In the current study Child–Pugh class and MELD score were both found to be predictors of survival, with 1-year survival rates in Child–Pugh classes A, B and C of 82%, 75% and 50%, respectively. Unlike this study, most of the existing clinical studies on treatment with doxorubicin DEB TACE have excluded patients in advanced stages, such as those with PVT and those in Child–Pugh class C.[5,24]

The presence of PVT has traditionally been considered as a contraindication for transarterial therapy.[9,10] However, it was not found to influence overall survival in the current study. Chung *et al.* and Lee *et al.* also demonstrated that PVT did not adversely affect survival after conventional chemoembolization if a proper technique was employed.[25,26] During transcatheter therapy for patients with PVT, super-selective embolization techniques were

Table 6 Prognostic factors for survival in different studies

Study	Year	*n*	Treatment	Prognostic factors
Mondazzi *et al.*[8]	1994	84	TACE	Age, total bilirubin, Child–Pugh score, tumour size, change in AFP
Livraghi *et al.*[16]	1995	746	PEI	Child–Pugh score, tumour stage
Allgaier *et al.*[17]	1998	132	TACE/PEI	Child–Pugh score, Okuda stage, PVT, AFP
Llado *et al.*[9]	2000	143	TACE	Ascites, AFP, tumour size, Child–Pugh score, pattern of Lipiodol intake, PVT
El Khaddari *et al.*[18]	2002	72	TACE	Child–Pugh score, interval between treatment
Grieco *et al.*[19]	2003	81	TACE	PVT, bilirubin, AFP, tumour size, Okuda, CLIP, BCLC
Goin *et al.*[20]	2005	121	Y-90 (Theraspheres)	Infiltrative tumour, AST/ALT > 5 ULN, tumour burden > 50%, albumin < 3.0 g/dl, bilirubin > 2 mg/dl
Sato *et al.*[21]	2008	229	Y-90 (Theraspheres)	Cirrhosis, infiltrative HCC, PVT, AFP, tumour burden

TACE, transarterial chemoembolization; PEI, percutaneous ethanol injection; AFP, alphafetoprotein; PVT, portal vein thrombosis; CLIP, Cancer of the Liver Italian Programme; BCLC, Barcelona Clinic Liver Cancer; Y-90, yttrium 90 radioembolization; HCC, hepatocellular carcinoma

used during this study, when feasible, which may partially explain the result.

The limitations of this study include its small number of patients and relatively short-term follow-up; thus the results must be taken as preliminary. Despite its limitations, the variables identified as prognostic factors are in concurrence with the risk factors for conventional chemoembolization. The results obtained in the study can be used as a guide to design further prospective studies.

Conclusions

Chemoembolization with doxorubicin DEB is a novel drug delivery system used as palliative treatment in patients with unresectable HCC. Appropriate patient selection remains the most important factor able to influence clinical outcome. Serum albumin level, bilirubin level, serum AFP, liver reserve (Child–Pugh class and MELD score), HCC staging (by Okuda staging, Milan criteria, CLIP score and BCLC staging) and PS as assessed by ECOG classification were found to be predictors of survival.

Conflicts of interest

None declared.

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