Factors Affecting Survival following Chemoembolization with Doxorubicin-eluting Microspheres for Inoperable Hepatocellular Carcinoma

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ABSTRACT

Purpose: To assess factors associated with better overall survival (OS) and progression-free survival (PFS) following chemoembolization with doxorubicin-eluting microspheres for inoperable hepatocellular carcinoma (HCC)

Materials and Methods: Data of 130 patients (104 men; median age, 62 y) with inoperable HCC who underwent successful DEB chemoembolization with 100–300 -μm LC Bead particles loaded with 50 mg doxorubicin per vial were reviewed following human research committee approval. Effects of various clinical, imaging, and response factors on OS and PFS were assessed by univariate Kaplan–Meier survival analysis. Multiple Cox regression with backward elimination was performed for terms found significant ($P \leq .05$) on univariate analysis.

Results: The number of DEB chemoembolization procedures per patient ranged from one to four (mean, 2 ± 1). The median PFS and OS were 5.7 months (95% confidence interval, 4.6–7.6 mo) and 14.7 months (95% confidence interval, 12.3–19.7 mo), respectively. On multivariate Cox regression, Cancer of the Liver Italian Program (CLIP) score of 1 or lower, necrosis of more than 50%, and response or stable disease per Response Evaluation Criteria In Solid Tumors after DEB chemoembolization were associated with better PFS. CLIP score of 1 or lower, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 1 or lower, absence of portal vein (PV) thrombosis, and necrosis greater than 50% following DEB chemoembolization were associated with better OS.

Conclusions: CLIP score of 1 or lower and necrosis of more than 50% are independent variables affecting PFS and OS after DEB chemoembolization, whereas absence of PV thrombosis and ECOG PS of 1 or lower affected OS but not PFS.

ABBREVIATIONS

AFP = α-fetoprotein, BCLC = Barcelona Clinic Liver Cancer, CLIP = Cancer of the Liver Italian Program, DEB = drug-eluting bead, EASL = European Association for the Study of the Liver, ECOG = Eastern Cooperative Oncology Group, HCC = hepatocellular carcinoma, OS = overall survival, PFS = progression-free survival, PS = performance status, PV = portal vein, RECIST = Response Evaluation Criteria In Solid Tumors, SD = stable disease

Conventional transarterial chemoembolization with a mixture of Lipiodol, chemotherapeutic drugs, and gelatin sponge or microspheres had been a mainstay of treatment for inoperable hepatocellular carcinoma (HCC) until the introduction of ablative procedures (1). Several randomized trials have demonstrated a survival benefit with conventional transarterial chemoembolization versus supportive care (2–5). Currently, it remains the treatment of choice for patients with Barcelona Clinic Liver Cancer (BCLC) stage B disease (6,7). Conventional transarterial chemoembolization is often associated with postembolization syndrome and is not well tolerated in patients with poor liver function or performance status (PS) (8,9). Chemoembolization with a new drug-delivery method that uses drug-eluting beads (DEBs) has been proposed as an alternative to conventional chemoembolization (10–12). Initial studies on

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pharmacokinetics of drug absorption and drug elution have demonstrated rapid uptake of doxorubicin by these beads and sustained, slow release of the drug in ionic solution (13). Several randomized trials comparing conventional chemoembolization versus chemoembolization with doxorubicin-eluting microspheres have demonstrated better tolerability and a superior safety profile of DEB chemoembolization, allowing for its use in a less fit population (14,15). A survival advantage associated with DEB chemoembolization versus conventional chemoembolization has not yet been established in randomized trials (14,15), but has been reported in one retrospective study (16). Factors predicting overall survival (OS) and progression-free survival (PFS) with DEB chemoembolization have not been well studied. The purpose of the present study was to determine the factors associated with better OS and PFS following DEB chemoembolization for inoperable HCC.

MATERIALS AND METHODS

This study was approved by human research committee of our institution, and the requirement to obtain informed consent for this retrospective analysis was waived. The study complied with the Health Insurance Portability and Accountability Act, and Society of Interventional Radiology reporting standards (17) were followed.

Patients

All patients who underwent a DEB chemoembolization procedure for inoperable HCC at a single institution from 2005 to 2011 were included in the study. The study cohort consisted of 130 patients with a median age of 62 years and a mean age of 63 years ± 10 years (standard deviation). There were 104 men and 26 women. The patient characteristics are shown in **Table 1**.

Clinical Diagnosis and Therapies

A diagnosis of HCC was made based on histopathologic findings in 92 patients (70.8%). In the remaining 38 (29.2%), HCC was diagnosed based on American Association for the Study of Liver Diseases imaging criteria (6). Forty-two patients (32.3%) received other therapies before DEB chemoembolization, including surgical resection in 12 patients (28.6%), thermal ablation in 19 (45.2%), conventional chemoembolization in three (7.1%), conventional chemoembolization and thermal ablation in one (2.4%), and systemic chemotherapy in seven (16.7%).

DEB Chemoembolization Procedure

DEBs. DEB chemoembolization procedures were performed according to a standardized protocol that was established in 2005 when we started to use DEBs for chemoembolization. LC Bead microspheres 100–300 μm in size (Biocompatibles, Surrey, United Kingdom) were used in this study. Each vial of beads (2 mL of beads) was loaded with 50 mg doxorubicin (Pfizer, New York, New York) per manufacturer recommendations, as essentially the same as

Table 1. Patient Characteristics (N = 130)

Characteristic	Value
Patient characteristics	
Male sex	104 (80)
Female sex	26 (20)
Age (y)	
Median	62
Mean ± SD	63 ± 10
Diagnosis of HCC	
Biopsy	92 (70.8)
Imaging	38 (29.2)
Imaging characteristics	
Unilobar	63 (48.5)
Bilobar	67 (51.5)
Unifocal	42 (32.3)
Multifocal	88 (67.7)
PV thrombosis	7 (5.4)
No PV thrombosis	123 (94.6)
Extrahepatic disease	11 (8.5)
Clinical staging	
Child–Pugh class	
A	87 (70)
B	41 (31.5)
C	2 (1.5)
BCLC stage	
A	12 (9.2)
B	33 (25.4)
C	81 (62.3)
D	4 (3.1)
Okuda stage	
1	72 (55.4)
2	57 (43.8)
3	1 (0.8)
ECOG PS	
0	48 (36.9)
1	63 (48.5)
2	15 (11.5)
3	4 (3.1)
CLIP score	
0	15 (11.5)
1	66 (50.8)
2	34 (26.2)
3	9 (6.9)
4	5 (3.8)
5	1 (0.8)
Laboratory characteristics	
Albumin ≥ 3 g/dL	114 (87.7)
INR < 1.5	119 (91.5)
Bilirubin < 1.5 mg/dL	98 (75.4)
AST ≤ 100 IU/L	82 (63.1)
ALT ≤ 100 IU/L	96 (73.9)
Therapies	
Previous therapies*	42 (32.3)
No. of DEB chemoembolizations	2 ± 1

Values in parentheses are percentages. Values presented as means ± SD where applicable. ALT = alanine aminotransferase, AST = aspartate aminotransferase, BCLC = Barcelona Clinic Liver Cancer, CLIP = Cancer of the Liver Italian Program, DEB = drug-eluting bead, ECOG = Eastern Cooperative Oncology Group, HCC = hepatocellular carcinoma, INR = International Normalized Ratio, PS = performance status, PV = portal vein, SD = standard deviation.

* Surgery, RF ablation, chemotherapy, or conventional transarterial chemoembolization.