Safety and Efficacy of Doxorubicin Drug-eluting Bead Transarterial Chemoembolization in Patients with Advanced Hepatocellular Carcinoma

Hasmukh J. Prajapati, MD, Renumathy Dhanasekaran, MD, Bassel F. El-Rayes, MD, John S. Kauh, MD, Shishir K. Maithel, MD, Zhengjia Chen, PhD, and Hyun S. Kim, MD

ABSTRACT

Purpose: To investigate the safety and efficacy of transarterial chemoembolization using doxorubicin drug-eluting beads (DEBs) in patients with Barcelona Clinic Liver Cancer (BCLC) C stage hepatocellular carcinoma (HCC).

Methods: Consecutive patients with initial staging of BCLC C HCC who received DEB transarterial chemoembolization over the last 5 years were studied. The study included 121 patients (mean age, 61.2 years old). Adverse events (AEs) after DEB transarterial chemoembolization were studied in detail and were recorded as per the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 criteria. Survivals were analyzed according to parameters from the time of first DEB transarterial chemoembolization. Kaplan-Meier method by log-rank test and Cox proportional hazard model were used for survival analysis.

Results: AEs occurred in 30.2% of patients. No AEs were greater than Common Terminology Criteria for Adverse Events grade III. Grade I and II AEs included nausea and vomiting in 7.8% of patients and abdominal pain in 23.8% of patients. Grade III AEs were noted in 1.06% of patients. There were no gastrointestinal or hepatic complications. There were no deaths within 30 days after DEB transarterial chemoembolization. The overall median survival was 13.5 months. Among the Child-Pugh class A patients, those without PVT and metastasis (28.9%) had better survival when treated with DEB transarterial chemoembolization than those with PVT and metastases (9.9%) (18.8 mo versus 4.4 mo, $P = .001$). Ascites, performance status, Okuda stage HCC, serum alpha fetoprotein levels, and etiologic factor for chronic liver disease predicted survival.

Conclusions: DEB transarterial chemoembolization appears to be a safe and effective treatment option for patients with BCLC C HCC. Patients with Child-Pugh class A without PVT and metastasis benefited most from DEB transarterial chemoembolization.

ABBREVIATIONS

AE = adverse event, AFP = alpha fetoprotein, BCLC = Barcelona Clinic Liver Cancer, DEB = drug-eluting bead, ECOG = Eastern Cooperative Oncology Group, HCC = hepatocellular carcinoma, PS = performance status, PVT = portal vein thrombosis, SHARP = Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol, TACE = transarterial chemoembolization

The Barcelona Clinic Liver Cancer (BCLC) staging system for hepatocellular carcinoma (HCC) is constructed on the basis of results of several cohort studies and randomized controlled trials by the Barcelona group (1,2). Advanced (BCLC C) stage HCC includes patients with symptomatic tumors or an invasive tumoral pattern (vascular invasion or extrahepatic spread) (1). Patients with advanced stage HCC have limited treatment options and a poor prognosis, owing to the underlying liver disease and lack of effective treatment options (2–4). The recommended treatment choice for patients with advanced stage HCC by BCLC staging is systemic therapy (2). Before the SHARP (Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol) trial (5,6), no systemic therapy had shown improved survival in patients with advanced HCC (7,8). More recent randomized trials have reported a modest median survival benefit of

From the Interventional Radiology and Image guided Medicine (H.J.P., R.D., H.S.K.), Hematology and Medical Oncology (B.F.E., J.S.K., H.S.K.), and Surgical Oncology, Department of Surgery (S.K.M., H.S.K.), and Biostatistics & Bioinformatics (Z.C.), Winship Cancer Institute, Emory University School of Medicine, 1364 Clifton Road NE, Suite AG-05, Atlanta, GA 30322. Received June 18, 2012; final revision received November 26, 2012; accepted November 28, 2012. **Address correspondence to** H.S.K.; E-mail: kevin.kim@emory.edu

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2.3 months and 2.8 months in patients with advanced stage HCC treated with sorafenib compared with placebo (5,6).

Transarterial chemoembolization with doxorubicin drug-eluting beads (DEBs) is a well-known locoregional treatment for HCC that has been evaluated by multiple randomized controlled studies. More recent DEB transarterial chemoembolization studies have shown fewer side effects and less toxicity compared with conventional transarterial chemoembolization and are at least as effective as conventional transarterial chemoembolization (9–11). One study demonstrated efficacy of conventional transarterial chemoembolization in advanced (BCLC C) stage HCC (12), and a randomized controlled study also suggested benefit of DEB transarterial chemoembolization in patients with HCC with advanced disease (9). The purpose of the present study was to investigate the safety and efficacy of DEB transarterial chemoembolization therapy in patients with advanced (BCLC C) stage HCC.

MATERIALS AND METHODS

This single institutional retrospective analysis of a prospective database was performed with patients' consent, approved by the local institutional review board and in compliance with the Health Insurance Portability and Accountability Act.

Study Objective

The primary objective of the study was to assess the safety and efficacy of treatment with DEB transarterial chemoembolization in patients with advanced (BCLC C) stage HCC. Secondary aims were to compare overall survival in subgroups based on different staging systems and the presence or absence of extrahepatic metastasis or portal vein thrombosis (PVT) or both and to determine prognostic factors for survival in patients with advanced stage HCC treated with DEB transarterial chemoembolization.

Patient Selection

Between January 2006 and December 2010, 204 consecutive patients with HCC were treated with DEB transarterial chemoembolization. Of these 204 patients with HCC, 121 patients (59.8%) had an initial presentation of advanced (BCLC C) stage HCC and were included in this study. The patients were staged with advanced (BCLC C) disease on the basis of Eastern Cooperative Oncology Group performance status (ECOG PS) in 52.9% of cases, portal vein invasion or PVT only in 23.9% of cases, metastasis only in 13.2% of cases, and both metastasis and PVT in 9.9% of cases (**Table 1**). Patients who received treatment with sorafenib were also included in the study. Cases were excluded from this analysis if the patient received bland embolization. The 119 patients had an initial outpatient clinic evaluation including pertinent medical and physical evaluations. The other two patients had in-patient consults and were assessed by an interventional radiologist for DEB transarterial chemoembolization (TACE) therapy. The ECOG PS of each patient was documented before the DEB transarterial chemoembolization procedure. Functional liver status was determined using the Child-Pugh criteria. The American Association for the Study of Liver Disease–Journal of the National Cancer Institute guidelines (3) were used to diagnose HCC. HCC was diagnosed if magnetic resonance (MR) imaging showed a mass with the typical vascular pattern of arterial enhancement and portal venous "washout." For the index lesions 1–2 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. Biopsies were performed for lesions with inconclusive features on imaging for pathologic confirmation.

DEB Transarterial Chemoembolization Procedure

There were 281 DEB transarterial chemoembolization procedures performed in 121 patients (mean, 2.33 ± standard deviation 1.71; range, 1–11). Large particles of 300–500 μm and 500-700 μm LC Beads (Biocompatibles, Farnham, Surrey, UK) were used in 22 patients, and small particles of 100–300 μm LC Beads were used in 99 patients (81.8%).The details of the procedure have been described elsewhere (13). The third-order or fourth-order branches of feeding vessels supplying the tumor were catheterized with a 2.8-F microcatheter (Renegade HI-FLO; Boston Scientific, Natick, Massachusetts) or a 2.1-F microcatheter (STC Renegade HI-FLO; Boston Scientific). The tumors were treated with a slow fluoroscopy-guided injection of iodinated contrast material mixed with 300–500 μm and 500–700 μm (before 2008) LC Beads or with 100–300 μm (from 2008–2010) LC Beads impregnated with 50 mg of doxorubicin in each vial. The first-order and second-order branches of the right or left hepatic arteries were kept patent and documented on angiography performed after completion of embolization. The endpoint for treatment included the administration of the two vials of DEBs 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 two vials of DEB transarterial chemoembolization, no additional embolization was performed despite persistent high flow within the tumor. In cases of arterioportal shunting, slurry absorbable gelatin sponge (Gelfoam; Pfizer, New York, New York) was injected before injection of DEBs. Otherwise, no additional embolization materials were used.

Follow-up

Patients with large tumors (>5 cm) or multifocal disease were retreated in 4 weeks, and the remaining patients were followed up in the clinic in 4 weeks with liver function tests and MR imaging of the liver. The National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 was used to report clinical adverse events (AEs) (14).