CLINICAL STUDY

Korean Multicenter Registry of Transcatheter Arterial Chemoembolization with Drug-Eluting Embolic Agents for Nodular Hepatocellular Carcinomas: Six-Month Outcome Analysis

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ABSTRACT

Purpose: To assess the efficacy and safety of transcatheter arterial chemoembolization with drug-eluting embolic (DEE) agents for nodular hepatocellular carcinoma (HCC).

Materials and Methods: The study design was a prospective multicenter registry-based, single-arm clinical trial that included 152 patients. One hundred three (67.8%) had a Child–Pugh class/score of A5, 114 (75.0%) had a performance status of 0, and 77 (50.7%) had Barcelona Clinic Liver Cancer (BCLC) stage A disease. The DEE chemoembolization procedures were performed with DC Bead particles loaded with doxorubicin solution. The primary endpoint of the study was 6-month tumor response assessed per modified Response Evaluation Criteria In Solid Tumors. Secondary endpoints were treatment safety and overall survival.

Results: At 1-month posttreatment assessment, complete response (CR) and objective response (OR; ie, CR or partial response) rates were 40.1% and 91.4%, respectively. At 6-month assessment, 121 patients remained for analysis, and CR and OR rates were 43.0% and 55.4%, respectively. The cumulative progression-free survival (PFS) rate at 6 months was 65.0%. Child–Pugh score, tumor multiplicity, and tumor size were independent predictors of PFS ($P = .020$, $P = .029$, and $P = .001$, respectively). There was no 30-day mortality. The overall 6-month survival rate was 97.4%. There were no grade 4 adverse events or laboratory changes. Serious adverse events were reported in 7.2% of patients, and persistent deterioration of liver function was observed in 3.9%. Prominent biliary injury was demonstrated in 19.7% of patients. No liver abscess was observed.

Conclusions: DEE chemoembolization for nodular HCC had an acceptable safety profile and acceptable 6-month tumor response and survival rates.

ABBREVIATIONS

BCLC = Barcelona Clinic Liver Cancer, CR = complete response, DEE = drug-eluting embolic, ECOG = Eastern Cooperative Oncology Group, HCC = hepatocellular carcinoma, IDR = intrahepatic distant recurrence, LTP = local tumor progression, PFS = progression-free survival, OR = objective response, PD = progressive disease, PES = postembolization syndrome, PR = partial response

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Transcatheter arterial chemoembolization with drug-eluting embolic (DEE) agents is an acknowledged treatment for hepatic malignancies, including hepatocellular carcinoma (HCC) and metastasis from extrahepatic malignancies (1). In an early randomized controlled trial in HCC (2), the authors concluded that DEE chemoembolization with doxorubicin achieved a better objective response (OR) in patients with advanced disease, and the incidences of serious liver toxicity and doxorubicin-related side effects were lower than with conventional transcatheter arterial chemoembolization with doxorubicin/oil emulsion followed by gelatin sponge administration. Subsequent prospective randomized trials comparing conventional chemoembolization and DEE chemoembolization in patients with HCC demonstrated less liver toxicity and postprocedural pain in the DEE chemoembolization group and similar local tumor response, recurrence, and survival (3,4). However, most reports concerning outcomes of DEE chemoembolization are from Western countries, and few document experience in clinical settings in Asian countries (5). Here we present the results of a prospective multicenter registry-based trial of DEE chemoembolization for HCC with doxorubicin in a large Asian population. The primary purpose of the study was to assess efficacy of treatment in terms of tumor response at 6-month follow-up. Secondary endpoints were to assess safety of the treatment (based on incidence and grade of adverse events) and survival.

MATERIALS AND METHODS

The study was designed as a prospective multicenter registry-based single-arm clinical trial with a target population of 200. The key inclusion and exclusion criteria are shown in **Table 1**. Five university hospitals participated in the trial, and patient recruitment was performed from May 2011 to April 2013. Institutional review board approval was obtained before the initiation of the study in each institution, and informed consent was obtained from all patients. The study was registered at *clincaltrials.gov* (ID code NCT01332669).

Baseline Demographic Data

Demographic characteristics of the study population are summarized in **Table 2**. The mean age of the patients was 61.4 years (range, 34–86 y), and 17.8% were women. Per Barcelona Clinic Liver Cancer (BCLC) staging, patients with a single tumor larger than 5 cm were allocated to stage A. There were 207 target tumors for per-lesion analysis, with mean and median diameters of 3.2 cm ± 2.1 (standard deviation) and 2.5 cm (interquartile range, 1.7–3.6 cm), respectively. Sixty-three tumors (30.4%) were smaller than 2 cm, 113 (54.6%) were between 2 and 5 cm in size, and 31 (15.0%) were larger than 5 cm.

DEE Chemoembolization Procedures

One vial of DEE agent (DC Bead; Biocompatibles UK, Farnham, United Kingdom) was loaded with 70–75 mg of doxorubicin solution (Adriamycin; Ildong, Seoul, Republic of Korea) for at least 2 hours (loading dose, 35–37.5 mg/mL of embolic agent), and the preparation was suspended in 20–50 mL of a mixture of normal saline solution and nonionic iodized contrast agent. The mixture was typically prepared at a 1:1 ratio of normal saline solution and contrast agent and adjusted to minimize precipitation of the embolic agent. Use of 100–300-μm DEE particles was recommended for a standard procedure. However, the choice of the actual amount of doxorubicin and embolic particle size was determined by operators in each institution in view of specific patient and tumor characteristics.

All procedures were performed by six board-certified radiologists specializing in interventional radiologic procedures with 5–20 years of experience as full-time interventional radiologists. Procedures were performed under fluoroscopy and angiography guidance, and rotational C-arm computed tomography (CT) or CT angiography was used based on operator decision. Celiac arteriography and superior mesenteric arteriography were performed with a 4- or 5-Fr angiographic catheter, and hepatic arteriography was performed after selection of the common or proper hepatic artery. A superselective (segmental or subsegmental) approach was used whenever possible by using a small-caliber microcatheter (2.0–2.4 Fr). The microcatheter was placed as distally as possible into the vessel supplying the tumor. DEE suspension was injected as slowly as possible to avoid reflux of the suspension and nontarget embolization. Recommended time for infusion was more than 20 minutes per vial. DEE agents were used for extrahepatic arteries supplying the tumors. The recommended embolization endpoint was near-stasis (ie, for the contrast column to clear within 2-5 heartbeats on completion arteriography).

In patients with large tumor burden, when hepatic arterial flow did not reach near-stasis after injection of two vials of DEE agents, a separate treatment session was recommended at a 2–4-week interval as a second session in the first cycle. When the separate treatment session was performed, the completion of the first cycle was defined as the date of the reference procedure. The actual technical aspects of the procedures were recorded, including the selectivity of DEE agent delivery and embolization endpoint. Selectivity of treatment was categorized as lobar, sectional, segmental, or subsegmental. The embolization endpoint was categorized as complete stasis, near-stasis, or no stasis.

Follow-up Imaging and Repeat Procedures

Regular clinical follow-up was performed with laboratory and imaging studies. Tumor response assessment