CLINICAL STUDY

Single- versus Triple-Drug Chemoembolization for Hepatocellular Carcinoma: Comparing Outcomes by Toxicity, Imaging Response, and Survival

Samdeep Mouli, MD, Ryan Hickey, MD, Bartley Thornburg, MD, Kent T. Sato, MD, Kush Desai, MD, Ahmed Gabr, MD, Joseph Ralph Kallini, MD, Halla Niemeri, MD, Sheetal Kircher, MD, Mary F. Mulcahy, MD, Al B. Benson III, MD, Ramona Gupta, MD, Riad Salem, MD, MBA, and Robert J. Lewandowski, MD

ABSTRACT

Purpose: To determine the efficacy of single- versus triple-drug chemoembolization for the treatment of hepatocellular carcinoma, as measured by toxicity, tumor response, time to progression (TTP), and overall survival (OS).

Materials and Methods: A single-center retrospective review was performed on 337 patients who underwent chemoembolization over a 14-year period; 172 patients underwent triple-drug conventional transarterial chemoembolization, and 165 patients underwent single-agent doxorubicin chemoembolization. Imaging characteristics and clinical follow-up after conventional transarterial chemoembolization were evaluated to determine TTP. Imaging response was determined per World Health Organization and European Association for the Study of Liver criteria. OS from time of first chemoembolization was calculated.

Results: Median TTP was similar between groups: 7.9 months (95% confidence interval [CI], 7.1–9.4) and 6.8 months (95% CI, 4.6–8.6) for triple- and single-drug regimens, respectively ($P > .05$). For single-agent conventional transarterial chemoembolization, median OS varied significantly by Barcelona Clinic for Liver Cancer (BCLC) stage: A, 40.8 months; B, 36.4 months; C, 10.9 months ($P < .01$). Median OS for triple-drug therapy also varied significantly by BCLC: A, 28.9 months; B, 18.1 months; C, 9.0 months ($P < .01$). Single-drug conventional transarterial chemoembolization demonstrated longer median OS compared with triple-drug therapy ($P < .05$) for BCLC A/B patients.

Conclusions: Single-agent chemoembolization with doxorubicin and ethiodized oil demonstrates acceptable efficacy as measured by TTP and OS. Results compare favorably with traditional triple-drug therapy.

ABBREVIATIONS

BCLC = Barcelona Clinic for Liver Cancer, CI = confidence interval, EASL = European Association for the Study of the Liver, ECOG = Eastern Cooperative Oncology Group, HCC = hepatocellular carcinoma, OS = overall survival, PVT = portal vein thrombosis, TTP = time to progression, WHO = World Health Organization

Most patients with hepatocellular carcinoma (HCC) present with advanced disease beyond curative treatments (1). Survival depends on tumor burden, underlying hepatic function, and the patient's performance status. In patients with unresectable intermediate-stage disease and preserved hepatic function, conventional transarterial chemoembolization is the standard of care per recognized guidelines (2). Treatment with conventional transarterial chemoembolization is supported by level I evidence from prospective randomized trials (3,4).

There is no consensus regarding the optimal conventional transarterial chemoembolization chemotherapy regimen; some combination of doxorubicin, cisplatin,

From the Department of Radiology, Section of Interventional Radiology (S.M., R.H., B.T., K.T.S., K.D., A.G., J.R.K., R.G., R.S., R.J.L.), and Department of Medicine, Division of Hematology and Oncology (H.N., S.K., M.F.M., A.B.B., R.S.), Robert H. Lurie Comprehensive Cancer Center, Northwestern University, 676 North St. Clair, Suite 800, Chicago, IL 60611. Received August 26, 2015; final revision received and accepted January 11, 2016. **Address correspondence to** R.J.L.; E-mail: r-lewandowski@northwestern.edu

None of the authors have identified a conflict of interest.

J Vasc Interv Radiol 2016; XX:■■■–■■■

http://dx.doi.org/10.1016/j.jvir.2016.01.135

and mitomycin has been used in the United States (5–8). However, the landmark trials demonstrating a survival benefit of conventional transarterial chemoembolization over best supportive care used single agents (3,4). The purpose of the present study was to determine the efficacy of a conventional transarterial chemoembolization regimen with a single drug (doxorubicin) compared with triple-drug therapy (doxorubicin, mitomycin, and cisplatin), as measured by clinical/biochemical toxicity, tumor response, time to progression (TTP), and overall survival (OS).

MATERIALS AND METHODS

Patients

Between January 1, 2000, and December 31, 2014, 337 patients underwent treatment with conventional transarterial chemoembolization for unresectable HCC at a single institution. Institutional review board approval was obtained, and this study was compliant with the Health Insurance Portability and Accountability Act.

Evaluation and Staging before Treatment

All patients underwent assessment before treatment, including history, physical examination, and laboratory analysis. Clinical criteria for treatment with conventional transarterial chemoembolization included (*a*) imaging or pathologic diagnosis of HCC, (*b*) Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, (*c*) bilirubin level $\leq$ 3.0 mg/dL (51.3 mmol/L), (*d*) segmental portal vein thrombosis (PVT) with hepatopetal flow, and (*e*) limited extrahepatic lymphadenopathy (periportal, cardiophrenic, or retroperitoneal lymph nodes $<$ 2.0 cm in diameter). Patients were excluded if they had a life expectancy $<$ 6 months, ECOG performance status $>$ 2, uncorrectable coagulopathy with an international normalized ratio $>$ 1.5, total bilirubin level $>$ 3.0 mg/dL, serum creatinine concentration $>$ 2.0 mg/dL, or uncorrectable thrombocytopenia with a platelet count $<$ 50,000/μL. Cirrhosis was defined as any of the following: nodular liver surface at imaging, portal hypertension, or evidence of cirrhosis at pathologic evaluation of a biopsy specimen. Portal hypertension was defined as the presence of either splenomegaly with thrombocytopenia (platelets $<$ 100,000/mL) or portosystemic shunts (patent umbilical veins, coronary/gastroesophageal varices, splenorenal shunts). Biopsy was performed to confirm HCC if the lesion did not meet standard imaging criteria (2). Baseline diagnostic imaging was performed by using contrast-enhanced magnetic resonance imaging or triphasic computed tomography (CT). Patients were staged using the Child-Pugh and Barcelona Clinic Liver Cancer (BCLC) classifications (9).

Baseline patient characteristics are summarized in Table 1. There were 172 patients in the triple-drug therapy group, and 165 patients in the single-drug therapy group. The groups were similar with respect to patient age and sex, with comparable etiologies of cirrhosis, tumor distribution, liver function (Child-Pugh), and cancer stage (BCLC). The only exception to this was a greater proportion of BCLC A patients in the single-drug group. The breakdown for BCLC stage by cohort was as follows: A, 62 (36%) for triple-drug therapy and 104 (63%) for single-drug therapy; B, 73 (42%) for triple-drug therapy and 51 (31%) for single-drug therapy; C, 37 (22%) for triple-drug therapy and 10 (6%) for single-drug therapy ($P = .93$).

Treatment

Treatment with conventional transarterial chemoembolization was based on consensus by a multidisciplinary team in HCC conference at our institution. Experienced operators from the dedicated interventional oncology program at our institution performed all treatments. On the day of treatment, patients underwent angiography to determine vascular anatomy and variants and to assess portal flow (10). For triple-drug therapy, chemotherapeutic agents (30 mg doxorubicin, 100 mg cisplatin, and 30 mg mitomycin) mixed with 10 mL ethiodized oil were injected at the segmental arterial level, followed by injection of 300–500 μm permanent embolic particles (Embospheres; BioSphere Medical, Inc, Rockland, Massachusetts). In 2011, there was a transition to single-drug therapy, and doxorubicin alone (calculated on the basis of body surface area [75 mg/m^2]), was mixed with 10 mL ethiodized oil and was injected at the segmental arterial level, followed by injection of 300–500 μm permanent embolic particles (Embospheres) (11). Embolic particles were infused until there was reduced anterograde flow with no further tumor blush seen (selective angiographic chemoembolization endpoint level 3) (12). All patients were admitted for management of postembolization syndrome. Additional chemoembolization sessions were performed if (*a*) the first treatment was thought to treat the lesion (or lesions) incompletely on cross-sectional images (represented by viable tumor), (*b*) the multifocality of disease did not allow complete targeting of tumor in one treatment session, (*c*) an alternate blood supply from parasitized hepatic arteries was identified at initial diagnostic angiography, or (*d*) there was progressive disease. In both groups, the overall median number of treatments were two per patient (range of one to five treatments) ($P > .05$). In patients who did undergo transplantation, median treatment number was one (range of one to five treatments) ($P > .05$).

Response Evaluation

Patients underwent imaging (triphasic CT or contrast-enhanced magnetic resonance imaging) 6 weeks after treatment to assess response in the treated lesions; they subsequently underwent imaging every 3 months.