CLINICAL STUDY

Comparison of Stable and Unstable Ethiodized Oil Emulsions for Transarterial Chemoembolization of Hepatocellular Carcinoma: Results of a Single-Center Double-Blind Prospective Randomized Controlled Trial

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ABSTRACT

Purpose: To compare the stability of stable and unstable water-in-oil emulsions and the efficacy and safety of these emulsions in a single-center, prospective double-blind trial of transarterial chemoembolization for hepatocellular carcinoma (HCC).

Materials and Methods: A total of 812 patients with inoperable HCC were randomized (stable emulsion, n = 402; unstable emulsion, n = 410). The 2 emulsions were prepared by using the same protocol except that different solvents were used for chemotherapy agents, including epirubicin, lobaplatin, and mitomycin C. The solvent in the stable emulsion arm was contrast medium and distilled water, and the solvent in the unstable emulsion arm was distilled water. The primary endpoint was overall survival (OS), and secondary endpoints were time to progression (TTP), tumor response, adverse events (AEs), and plasma epirubicin concentrations.

Results: In vitro, stable emulsions did not occur until 1 day, and unstable emulsions, with a lower peak plasma concentration ($P = .001$) in vivo, exhibited rapid separation of the oil and aqueous phases after 10 minutes. Median OS times in the stable and unstable emulsion arms were 17.7 and 19.2 months, respectively ($P = .81$). No differences were found in TTP, tumor response, and AEs except for myelosuppression (anemia, 3.5% vs 7.6%; thrombocytopenia, 11.5% vs 17.7%), which was significantly more severe and frequent in the unstable emulsion arm ($P = .013$).

Conclusions: Chemoembolization is equally effective with the use of stable and unstable emulsions, but the use of a stable emulsion has the advantage of less myelosuppression and a favorable pharmacokinetic profile.

ABBREVIATIONS

AE = adverse event, AUC = area under the curve, CI = confidence interval, C_{max} = maximum concentration, HCC = hepatocellular carcinoma, HR = hazard ratio, OS = overall survival, PK = pharmacokinetic, PVA = polyvinyl alcohol, TTP = time to progression, W/O = water-in-oil

Transarterial chemoembolization is dependent on the targeted delivery of anticancer agents to a hepatocellular carcinoma (HCC), followed by blockage of the blood vessels by an embolic agent (1,2). Ethiodized oil, which has long been used as a carrier for anticancer agents to HCC neoplasms (3,4), shows selective uptake and retention in

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None of the authors have identified a conflict of interest.

Appendix A and Figures E1 and E2 are available online at www.jvir.org.

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EDITORS' RESEARCH HIGHLIGHTS

- This single-center, double-blind randomized controlled study investigated tumor radiologic response, time to progression (TTP), overall survival (OS; primary endpoint), drug pharmacokinetic (PK) data, and adverse events (AEs) following conventional transarterial chemoembolization treatment of surgically unresectable Barcelona Clinic Liver Cancer stage A/B hepatocellular carcinoma (HCC) using stable (3:1 ethiodized oil–to–aqueous phase consisting of 5:1 iodinated contrast medium to water) versus unstable (3:1 ethiodized oil–to–aqueous phase consisting of water) emulsions of ethiodized oil and drug (epirubicin, lobaplatin, and mitomycin C).
- A total of 812 patients were enrolled between 2011 and 2015, with 402 and 410 randomly assigned to the stable and unstable ethiodized oil/drug emulsion treatment arms, respectively; features of the study populations in the trial arms were generally well matched (eg, tumor size and chemoembolization session number), save for a slight female preponderance in the unstable emulsion arm (12% vs 8%; $P = .03$).
- Major findings included similar modified Response Evaluation Criteria In Solid Tumors response rates at 12 weeks after treatment (stable emulsion arm, 43% objective response vs 40% in unstable emulsion arm; $P = .46$), similar TTP (stable emulsion arm, 5.2 months vs 4.3 months in unstable emulsion arm; $P = .27$), and similar OS (stable emulsion arm, 17.8 months vs 19.2 months in unstable emulsion arm; $P = .81$) in the stable and unstable ethiodized oil/drug emulsion treatment arms.
- PK and AE analysis showed higher systemic levels of epirubicin after chemoembolization with the use of an unstable emulsion (maximum concentrations, 754 ng/mL vs 1,520 ng/mL in unstable emulsion arm).

hyperarterialized HCCs, achieving the goal of sustained drug delivery in HCC (5,6). However, the mixture of anticancer agents and ethiodized oil is unstable, exhibiting rapid separation of the oil and aqueous phases because most anticancer agents are water-soluble (7).

In an effort to form stable emulsions of anticancer agents with ethiodized oil, a stable emulsion was developed as follows: anticancer agents were dissolved in a fluid with a specific gravity equivalent to that of ethiodized oil, and then a stable water-in-oil (W/O) emulsion, which could allow slow, sustained release of anticancer agents, could be obtained by mixing the ethiodized oil and anticancer agent solution at a 2–3:1 ratio (8,9). Previous preclinical and small nonrandomized studies (4,7,9–16) have suggested that, compared with an unstable emulsion, a stable W/O emulsion could be selectively retained in HCC when injected into the hepatic artery and could improve the pharmacokinetic (PK) profiles and outcomes of chemoembolization.

Although various stable emulsions and optimal ratios have been developed (8,9,17), recent studies have continued to use unstable emulsions (18) or a mixture of anticancer agents with ethiodized oil at a volume ratio of 1:1 (19,20). Additionally, most clinical studies of sustained drug delivery have not carefully described the types of ethiodized oil emulsions used or the mixing steps (19,21,22). Also, we are aware of no prospective trial that has demonstrated the superiority of chemoembolization with the use of a stable W/O emulsion compared with an unstable W/O emulsion. The present study is a randomized, double-blind study to compare the safety, PK parameters, and efficacy of chemoembolization with a stable W/O emulsion versus an unstable W/O emulsion.

MATERIALS AND METHODS

Study Design

This study was a prospective single-center, double-blind, randomized phase III trial conducted and approved by the institutional review board at the authors' institution. The study data were monitored independently by the department of clinical research at the center. The study has been registered at ClinicalTrials.gov under identifier NCT01259414.

Inclusion and Exclusion Criteria

Patients who were older than 17 years with a diagnosis of Barcelona Clinic Liver Cancer stage A/B HCC based on the diagnostic criteria for HCC used by the European Association for the Study of the Liver (23) were screened for trial eligibility by the same multidisciplinary team composed of hepatologists, interventional radiologists, oncologists, and general surgeons. The inclusion criteria also included (*i*) tumors not amenable to any curative treatments, (*ii*) no cirrhosis or only Child–Pugh class A disease, and (*iii*) the following laboratory parameters: neutrophil count $\geq$ 1,500/μL, platelet count $\geq$ 60,000/μL, hemoglobin level $\geq$ 8.5 g/dL, total bilirubin level $\leq$ 1.5 mg/dL, and serum albumin level $\geq$ 3.5 g/dL. Patients were excluded from the study if they had (*i*) severe underlying cardiac (ejection fraction $\leq$ 50%) or renal diseases (serum creatinine level $\geq$ 1.5 $\times$ the upper limit of normal) or (*ii*) obstructive jaundice.

Random Assignment, Masking, and Baseline Demographic Data

After hepatic artery angiography, the patients were randomly allocated to undergo chemoembolization with a stable or unstable W/O emulsion by opening a sealed envelope. The computer-generated block randomization sequence was created with a 1:1 allocation by an independent organization. Random assignment was stratified by Barcelona Clinic Liver Cancer stage. According to the allocation, the 2 types of emulsions were prepared by the attending nurse and kept in opaque syringes before administration. The nurse was instructed not to reveal the type of emulsion. The investigators, chemoembolization operators, and patients remained blinded to the type of emulsions administered.

Between January 1, 2011, and December 1, 2015, 812 patients were randomly assigned to receive the stable