Sodium Cholate Bile Acid-Stabilized Ferumoxytol-Doxorubicin-Lipiodol Emulsion for Transcatheter Arterial Chemoembolization of Hepatocellular Carcinoma

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ABSTRACT

Purpose: To develop bile acid-stabilized multimodal magnetic resonance (MR) imaging and computed tomography (CT)-visible doxorubicin eluting lipiodol emulsion for transarterial chemoembolization of hepatocellular carcinoma (HCC).

Materials and Methods: Ferumoxytol, a US Food and Drug Administration-approved iron oxide nanoparticle visible under MR imaging was electrostatically complexed with doxorubicin (DOX). An amphiphilic bile acid, sodium cholate (SC), was used to form a stable dispersion of ferumoxytol-DOX complex in lipiodol emulsion. Properties of the fabricated emulsion were characterized in various component ratios. Release kinetics of DOX were evaluated for the chemoembolization applications. Finally, in vivo multimodal MR imaging/CT imaging properties and potential therapeutic effects upon intra-arterial (IA) infusion bile acid-stabilized ferumoxytol-DOX-lipiodol emulsion were evaluated in orthotopic McA-Rh7777 HCC rat models.

Results: DOX complexed with ferumoxytol through electrostatic interaction. Amphiphilic SC bile acid at the interface between the aqueous ferumoxytol-DOX complexes and lipiodol enabled a sustained DOX release (17.2 ± 1.6% at 24 hours) at an optimized component ratio. In McA Rh7777 rat HCC model, IA-infused emulsion showed a significant contrast around tumor in both T2-weighted MR imaging and CT images ($P = .044$). Hematoxylin and eosin and Prussian blue staining confirmed the local deposition of IA-infused SC bile acid-stabilized emulsion in the tumor. The deposited emulsion induced significant increases in TUNEL (terminal deoxynucleotidyl transferase dUTP nick end labeling) stain-positive cancer cell apoptosis compared to those in a group treated with the nonstabilized emulsion.

Conclusions: SC bile acid-stabilized ferumoxytol-DOX-lipiodol emulsion demonstrated sustained drug release and multimodal MR imaging/CT imaging capabilities. The new lipiodol-based formulation may enhance the therapeutic efficacy of chemoembolization in HCC.

ABBREVIATIONS

CNR = contrast-to-noise ratio, DOX = doxorubicin, HCC = hepatocellular carcinoma, IA = intra-arterial infusion, SC = sodium cholate, W/O = water-in-oil emulsion

Since the early 1980s, lipiodol-based transarterial chemoembolization with doxorubicin (DOX) has been used as the standard of care for studies comparing other intra-arterial (IA) therapies (e.g., drug-eluting beads, radioembolization) or systemic chemotherapy (sorafenib) in patients with intermediate or advanced hepatocellular carcinoma (HCC) (1). Due to its properties of radiopacity, plasticity, drug delivery, and embolization, lipiodol has been widely adapted (2–4).

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Figures E1–E6 can be found by accessing the online version of this article on *www.jvir.org* and clicking on the Supplemental Material tab.

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