Idarubicin-Loaded ONCOZENE Drug-Eluting Embolic Agents for Chemoembolization of Hepatocellular Carcinoma: In Vitro Loading and Release and In Vivo Pharmacokinetics

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ABSTRACT

Purpose: To present in vitro loading and release characteristics of idarubicin with ONCOZENE (CeloNova BioSciences, Inc, San Antonio, Texas) drug-eluting embolic (DEE) agents and in vivo pharmacokinetics data after transarterial chemoembolization with idarubicin-loaded ONCOZENE DEE agents in patients with hepatocellular carcinoma.

Materials and Methods: Loading efficacy of idarubicin with ONCOZENE DEE agents 100 μm and DC Bead (Biocompatibles UK Ltd, Farnham, United Kingdom) DEE agents 100–300 μm was monitored at 10, 20, and 30 minutes loading time by high-pressure liquid chromatography. A T-apparatus was used to monitor the release of idarubicin from the two types of DEE agents over 12 hours. Clinical and 24-hour pharmacokinetics data were recorded after transarterial chemoembolization with idarubicin-loaded ONCOZENE DEE agents in four patients with unresectable hepatocellular carcinoma.

Results: Idarubicin loading in ONCOZENE DEE agents was > 99% at 10 minutes. Time to reach 75% of the release plateau level was 37 minutes ± 6 for DC Bead DEE agents and 170 minutes ± 19 for ONCOZENE DEE agents both loaded with idarubicin 10 mg/mL. After transarterial chemoembolization with idarubicin-loaded ONCOZENE DEE agents, three partial responses and one complete response were observed with only two asymptomatic grade 3 biologic adverse events. Median time to maximum concentration for idarubicin in patients was 10 minutes, and mean maximum concentration was 4.9 μg/L ± 1.7. Mean area under the concentration-time curve from 0–24 hours was equal to 29.5 μg.h/L ± 20.5.

Conclusions: ONCOZENE DEE agents show promising results with very fast loading ability, a favorable in vivo pharmacokinetics profile with a sustained release of idarubicin during the first 24 hours, and encouraging safety and responses. Histopathologic and clinical studies are needed to evaluate idarubicin release around the DEE agents in tumor tissue and to confirm safety and efficacy.

ABBREVIATIONS

AE = adverse event, $AUC_{0-24\ h}$ = area under the concentration-time curve from 0–24 hours, C_{max} = maximum concentration, DEE = drug-eluting embolic, HCC = hepatocellular carcinoma, LLOQ = lower limit of quantification, MDR = multidrug resistance, PK = pharmacokinetic, T_{max} = time to maximum concentration

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S.R., T.P., and J.B. are employees of CeloNova BioSciences, Inc. None of the other authors have identified a conflict of interest.

J Vasc Interv Radiol 2015; 26:262–270

http://dx.doi.org/10.1016/j.jvir.2014.08.021

Drug-eluting embolic (DEE) agents, capable of slow release of an anticancer drug to the tumor as well as embolization, were developed in the 2000s (1,2) for transarterial chemoembolization of hepatocellular carcinoma (HCC). The only randomized trial (PRECISION V) to compare transarterial chemoembolization with doxorubicin-eluting embolic agents with conventional transarterial chemoembolization using ethiodized oil as the vector in patients with HCC demonstrated a lower systemic effect of doxorubicin in the transarterial chemoembolization with DEE agents arm. Nonetheless, the primary endpoint (ie, tumor response at 6 mo) was not

Table 1. Study Endpoints

	Endpoint	Method
In vitro experiments		
ONCOZENE 100 μm 1 mL with idarubicin 1 mg/mL, 5 mg, 10 mg, 15 mg (#1)	Loading efficacy	High-pressure liquid chromatography*
DC Bead 100–300 μm 1 mL with idarubicin 1 mg/mL, 10 mg (#2)		
#1 + #2	Size before/after loading	Optical microscopy†
#1 + #2	Release degree	T-apparatus‡
In vivo experiment (transarterial chemoembolization procedure)		
ONCOZENE 100 μm 2 mL with idarubicin 10 mg (4 patients)	Efficacy	mRECIST criteria
	Safety	NCI CTCAE
	PK; C_{max}, $AUC_{0–24}$	Blood samples

$AUC_{0–24}$ = area under the concentration-time curve from 0–24 hours; mRECIST = modified Response Evaluation Criteria In Solid Tumors; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

*After the designated amount of idarubicin was added to the DEE agents, the mixture was agitated every 5 minutes for 30 minutes. Loading efficacy (loaded amount/added amount) was monitored at 10, 20, and 30 minutes loading time by high-pressure liquid chromatography (column, SUPELCOSIL LC-18-DB [Sigma-Aldrich, St Louis, Missouri]; flow, 1.5 mL/min; λ = 485 nm; mobile phase, pH = 4.32, 1:1 mixture of 0.1 M aqueous ammonium acetate and acetonitrile; Flexar [PerkinElmer, Waltham, Massachusetts]) and evaluated with idarubicin calibration curves, which were linear in the concentration range of up to 10 μg/mL with a determination coefficient $R^2 > 0.999$.

†The sizes of the DEE agents were analyzed before and after idarubicin loading (AxioVision 4.8; Carl Zeiss Microscopy GmbH, Jena, Germany).

‡After 30 minutes of loading time, the supernatant was removed, and the DEE agents were transferred into a United States Pharmacopeia type 4 flow-through apparatus (SOTAX AG; Allschwil, Switzerland). Release degree of idarubicin (released amount/loaded amount) was measured under controlled temperature conditions of 37°C, using 1 L isotonic saline release medium (B. Braun AG, Melsungen, Germany), a 5 mL/min flow rate, and continuous monitoring by ultraviolet-visible spectrophotometry (λ = 485 nm). When a release plateau (first release) was reached, the drug-saturated release medium was replaced with another 1 L of isotonic saline (second release). Time to reach 75% of release plateau level was defined as the time to reach 75% of the first release plateau level. Any idarubicin remaining in the DEE agents after these release procedures was extracted with nonisotonic medium (high-pressure liquid chromatography mobile phase).

superior in the transarterial chemoembolization with DEE agents arm (51.6% vs 43.5%, $P = .11$) (3). It is necessary to optimize transarterial chemoembolization therapy (vector, anticancer drug, dose) to improve response and survival.

A recent in vitro screening study demonstrated that idarubicin was the most cytotoxic drug on HCC cell lines (4). This improved cytotoxicity results from both better penetration of idarubicin through the lipid double layer of tumor cells and the ability of idarubicin to overcome the multidrug resistance (MDR) system, which is very active in HCC cells (5). Use of idarubicin-loaded DC Bead (Biocompatibles UK Ltd, Farnham, United Kingdom) DEE agents was evaluated in a phase I trial (6), which showed promising efficacy in HCC patients.

With regard to the vector, ONCOZENE (CeloNova BioSciences, Inc, San Antonio, Texas) is a novel spherical drug-releasing delivery embolization system. The DEE agents consist of a hydrogel core made of sodium polymethacrylate, which is negatively charged and capable of being loaded with positively charged anticancer drugs, such as doxorubicin hydrochloride or idarubicin hydrochloride. The hydrogel core is coated with an inorganic polymer, poly[bis(trifluroexthoxy)phosphazene] (Polyzene-F; CeloNova BioSciences, Inc), to create a biocompatible outer shell. The drug release is diffusion-driven from the inner core to the surface for release. These new DEE agents are small with tightly calibrated sizes (40 μm, 75 μm, 100 μm). In a rabbit liver tumor model, it was shown after injection of 40 μm ONCOZENE DEE agents loaded with irinotecan that time at the drug maximum concentration (C_{max}) was prolonged (7). This time period was longer than that reported with DC Bead (8).

The purpose of the present study was to test idarubicin with ONCOZENE DEE agents by exploring in vitro loading and release characteristics and in vivo pharmacokinetics (PK) data after transarterial chemoembolization with idarubicin-loaded ONCOZENE DEE agents in patients with HCC. In vitro experiments were also conducted in the same conditions with DC Bead, the most commonly used DEE agent for transarterial chemoembolization of HCC.

MATERIALS AND METHODS

In Vitro Experiments

Loading efficacy for the drug (loaded amount/added amount), DEE agent size modification after loading, and