Phase I Study of Heat-Deployed Liposomal Doxorubicin during Radiofrequency Ablation for Hepatic Malignancies

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ABSTRACT

Purpose: A phase I dose escalation study was performed with systemically delivered lyso-thermosensitive liposomal doxorubicin (LTLD). The primary objectives were to determine the safe maximum tolerated dose (MTD), pharmacokinetic properties, and dose-limiting toxicity (DLT) of LTLD during this combination therapy.

Materials and Methods: Subjects eligible for percutaneous or surgical radiofrequency (RF) ablation with primary (n = 9) or metastatic (n = 15) tumors of the liver, with four or fewer lesions as large as 7 cm in diameter, were included. RF ablation was initiated 15 minutes after starting a 30-minute intravenous LTLD infusion. Dose levels between 20 mg/m^2 and 60 mg/m^2 were evaluated. Magnetic resonance imaging, positron emission tomography, and computed tomography were performed at predetermined intervals before and after treatment until evidence of recurrence was seen, administration of additional antitumor treatment was performed, or a total of 3 years had elapsed.

Results: DLT criteria were met at 60 mg/m^2, and the MTD was defined as 50 mg/m^2. RF ablation was performed during the peak of the plasma concentration–time curve in an effort to yield maximal drug deposition. LTLD produced reversible, dose-dependent neutropenia and leukopenia.

Conclusions: LTLD can be safely administered systemically at the MTD (50 mg/m^2) in combination with RF ablation, with limited and manageable toxicity. Further evaluation of this agent combined with RF ablation is warranted to determine its role in the management of liver tumors.

ABBREVIATIONS

ALT = alanine aminotransferase, AST = aspartate aminotransferase, AUC = area under the plasma concentration–time curve, $AUC_{0-\infty}$ = area under the plasma concentration–time curve from time 0 to infinity, DLT = dose-limiting toxicity, LTLD = lyso-thermosensitive liposomal doxorubicin, MTD = maximum tolerated dose, PET = positron emission tomography, RF = radiofrequency

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Thermal ablation techniques such as radiofrequency (RF) ablation have been widely used for unresectable liver tumors; however, residual or recurrent disease is often found at the treatment margin. A wide variability in local failure rates has been reported with RF ablation systems for the treatment of primary and metastatic liver tumors (1–4). For example, local progression rates after RF ablation for tumors smaller than 3 cm in diameter ranges from 1.8% to 52.8% (3–6). For tumors larger than 3 cm, however, the local failure rate for RF ablation increases markedly, to as high as 75% (1–4,7–9). In a metaanalysis of 5,224 liver tumors treated by RF ablation, tumor size larger than 3 cm was one of the most important risk factors for local recurrence (10). Equipment and techniques for thermal ablation continue to evolve in an effort to create more uniform and larger thermal lesions to address treatment failure at the margin.

Recurrences at the margins of the treated lesions are most likely caused by areas of untreated microscopic disease. It is possible that this zone of microscopic disease could be effectively treated by combining chemotherapy with RF ablation (11). The challenge is to minimize the systemic toxicity of chemotherapy and to maximize its local delivery to the region immediately surrounding the liver tumor during RF ablation, which remains viable, but is exposed to nonlethal increases in temperature. In related experiments, mild hyperthermia (39°C–40°C) not only improved the release of doxorubicin encapsulated in lyso-thermosensitive liposomes, but also increased doxorubicin attachment to DNA and RNA of tumor tissue in a human tumor xenograft model (12). In addition, more than 10 times more doxorubicin was detected just outside the thermal lesion than in remote unheated tissue in swine liver in vivo when lyso-thermosensitive liposome–encapsulated doxorubicin was administered intravenously during RF ablation (13). Local image-guided drug delivery is possible by combining ablative devices with heat-deployed chemotherapy. Lyso-thermosensitive liposomal doxorubicin (LTLD; ThermoDox; Celsion, Lawrenceville, NJ) has been developed to release doxorubicin at temperatures greater than 39.5°C, the same temperature range as is present in tissue immediately surrounding the thermal ablation zone, in both mathematical modeling and in vivo studies (14).When LTLD is combined with RF ablation, the drug may be deposited precisely in the location of the most common treatment failure: this thermal margin. There are very limited data on RF ablation combined with systemic or regional therapeutic agents, but previous work suggests that the use of non–heat-sensitive liposomal doxorubicin may increase the volume of ablation (11). Previous work showed that doxorubicin remains cytotoxic in tissue culture when it is heated in the typical range of time and temperature as with RF ablation (Online Supplementary Material; available at *www.jvir.org*). This drug-plus-device paradigm of ablative devices combined with heat-deployed chemotherapy directly addresses the high rate of local failure of RF ablation, especially in large tumors, by selectively depositing chemotherapy at the thermal margin, where it is most needed.

To evaluate the safety and feasibility of this drug-plus-device combination, a phase I dose-escalation study of LTLD administered during RF ablation of unresectable hepatic malignancies was performed. The primary objectives were to determine the safe maximum tolerated dose (MTD), pharmacokinetic properties, and dose-limiting toxicity (DLT) of LTLD administered systemically in conjunction with thermal ablation.

MATERIALS AND METHODS

All patients provided written informed consent, and the study was approved by the institutional review boards and the United States Food and Drug Administration as part of an Investigational New Drug evaluation.

Patient Selection

Patients with unresectable primary or metastatic liver neoplasms, with no more than four lesions each with diameters no greater than 7 cm, were eligible. Systemic therapy for extrahepatic disease was not allowed 21 days before enrollment or 28 days after treatment. Standard exclusion criteria for doxorubicin use and laboratory values were defined (Online Supplementary Material; available at *www.jvir.org*).

Drug Formulation and Treatment Schema

A single on-site pharmacist prepared the LTLD to the specified concentration according to the manufacturer's guidelines. Additional details may be found in Online Supplementary Material (available at *www.jvir.org*). Dosing was carried out based on the subject's body surface area (in m^2) calculated by using the Boyd formula. A 3 + 3 dose escalation design was used, and six dose levels were planned: 20, 30, 40, 50, 60, and 70 mg/m^2, with three to six patients per dose level. The MTD was defined as the dose at one level below the maximum achieved dose at which two patients exhibited DLT (**Table 1**). When the MTD had been defined, additional patients were entered at the MTD, for a total of six patients at that dose level. Therefore, no more than one in six patients would exhibit DLT at the MTD.

Preprocedural Protocol

Standard pretreatment evaluation included contrast-enhanced computed tomography (CT), recording of vital signs, serum chemistry analysis, complete blood counts, liver function tests, coagulation panel analysis, electrocardiography, and a multigated acquisition scan or echocardiography. Maximum lifetime dose of doxorubicin was limited to less than 500 mg/m^2.

All patients received prophylaxis against immediate