Curr Oncol, Vol. 20, pp. e274-277; doi: http://dx.doi.org/10.3747/co.20.1266

CASE REPORT

Liposomal doxorubicin plus radiofrequency ablation for complete necrosis of a hepatocellular carcinoma

C.W. Hong BS,*† *S.K. Libutti* MD,‡§ *and B.J. Wood* MD*§

ABSTRACT

Radiofrequency ablation (RFA) is a standard treatment for small, unresectable hepatocellular carcinomas (HCCs). However, RFA for larger tumours is less successful, and intravenous lyso-thermosensitive liposomal doxorubicin during RFA is one technique postulated to potentially address that limitation. This drug-plus-device combination therapy was used to completely treat a HCC in a patient who underwent liver transplantation 79 days later.

KEY WORDS

RFA, ablation, hepatocellular carcinoma, doxorubicin, liposomes

1. INTRODUCTION

Surgical resection for hepatocellular carcinoma (HCC) is not feasible for most patients because of inadequate hepatic reserve, geography of tumour burden, or tumour location[1]. In meta-analyses comparing radiofrequency ablation (RFA) with percutaneous ethanol injection, RFA has shown better survival and effectiveness[2], and it is currently the most widely used ablative technique for unresectable HCC. However, the use and success of RFA is generally limited by the size of the lesion, with significantly higher failure rates being seen with lesions larger than 3 cm[3].

It has been suggested that augmenting thermal effects with local heat-deployed chemotherapy in the treatment margin (where untreated microscopic disease may remain untreated) could improve the effectiveness of RFA. Lyso-thermosensitive liposomal doxorubicin [LTLD (ThermoDox: Celsion Corporation, Lawrenceville, NJ, U.S.A.)] deploys its cargo at temperatures greater than 39.5°C. Drug concentration is highest within a centimetre of the ablative zone[4], and markedly higher drug levels are present in and around heated tissue in rabbit Vx2 tumours exposed to high-intensity focused ultrasound[5]. In a phase I dose-escalation clinical trial of RFA with LTLD, a patient underwent transplantation after the combined approach of RFA plus drug[6]. Pathology showed no residual tumour at the treatment site.

2. CASE DESCRIPTION

A 53-year-old man with cirrhosis and chronic hepatitis C for 42 years originally presented with severe jaundice and also had a remote history of intravenous drug use, alcohol abuse, and smoking. A routine liver biopsy 5 years pre-ablation showed bridging fibrosis and a high hepatitis C polymerase chain reaction titre of 690,000 copies per millilitre. His hepatitis C was treated with pegylated interferon and ribavirin in a clinical trial. Normalization of serum aminotransferases was seen with that treatment, although he remained positive for hepatitis C by polymerase chain reaction.

A solid 3.2-cm mass arising from the anterior right lobe of the liver was discovered during routine ultrasonography screening (Figure 1), together with fatty infiltration of the liver. The mass was hypoechoic and showed faint vascularity on both

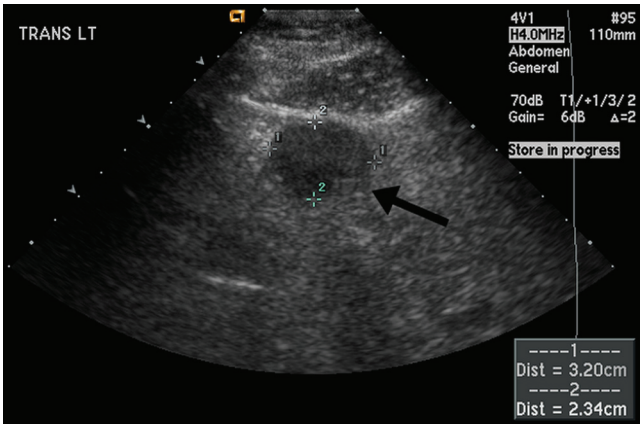

FIGURE 1 *Screening ultrasonography shows a 3.2-cm hypoechoic mass (arrow) along the hepatic capsule.*

ultrasonography and arterial-phase computed tomography (CT) [Figure 2(A)] and on magnetic resonance imaging.

Ultrasound-guided core needle biopsies under local anesthesia showed HCC, Edmondson grade 3 or 4. The biopsy also demonstrated moderately active and bridging fibrosis, concurrent steatohepatitis, portal chronic inflammatory infiltrate, and Mallory body formation; however, vascular invasion was not seen. Radiofrequency ablation was performed in conjunction with LTLD under general anesthesia. The ThermoDox was administered intravenously over 30 minutes at 20 mg/m^2 for a total dose of 41.9 mg in 291 mL 5% dextrose. The RFA, which was initiated 15 minutes after the start of drug infusion, used standard algorithms, with three slightly overlapping treatment zones, a commercial 200 W generator, and a water-cooled electrode (Covidien, Boulder, CO, U.S.A.). After completion of ablation, contrast-enhanced CT imaging showed a 34×25-mm thermal lesion of devascularization [Figure 2(B)].

To prevent potential systemic drug release, the patient's body temperature was monitored. Had his body temperature risen above 38°C, the patient would have been cooled with a full-body cooling blanket (Gaymar Industries, Orchard Park, NY, U.S.A.) and additional cooling blankets (Cincinnati Sub-Zero, Cincinnati, OH, U.S.A.) wrapped around his thighs, covering the grounding pads. Other than a mild drop in hematocrit (which may have been a result of dilution and hydration), the patient's complete blood count was within normal limits. His post-therapy alanine aminotransferase level increased to 115 IU/L from 52 IU/L, and his aspartate aminotransferase increased to 116 IU/L from 54 IU/L. This increase in serum liver enzymes reflecting liver injury is expected after RFA[7], and in this case, levels fell to baseline after a week. Contrast-enhanced CT at 1 month post RFA showed a 53×29-mm devascularized region [Figure 2(C)].

The patient was placed high on the list for liver transplantation as a curative therapy 75 days post RFA, and the procedure was performed 4 days later. Pathology evaluation of the explant showed a surface studded with multiple regenerative and cirrhotic nodules of varying size, and a 4.9-cm maximum-dimension "cautery" effect, with no tumour identified in the RFA bed. A previously unsuspected and untreated second tumour, clandestine on all imaging modalities, was incidentally discovered in the caudate lobe of the explant.

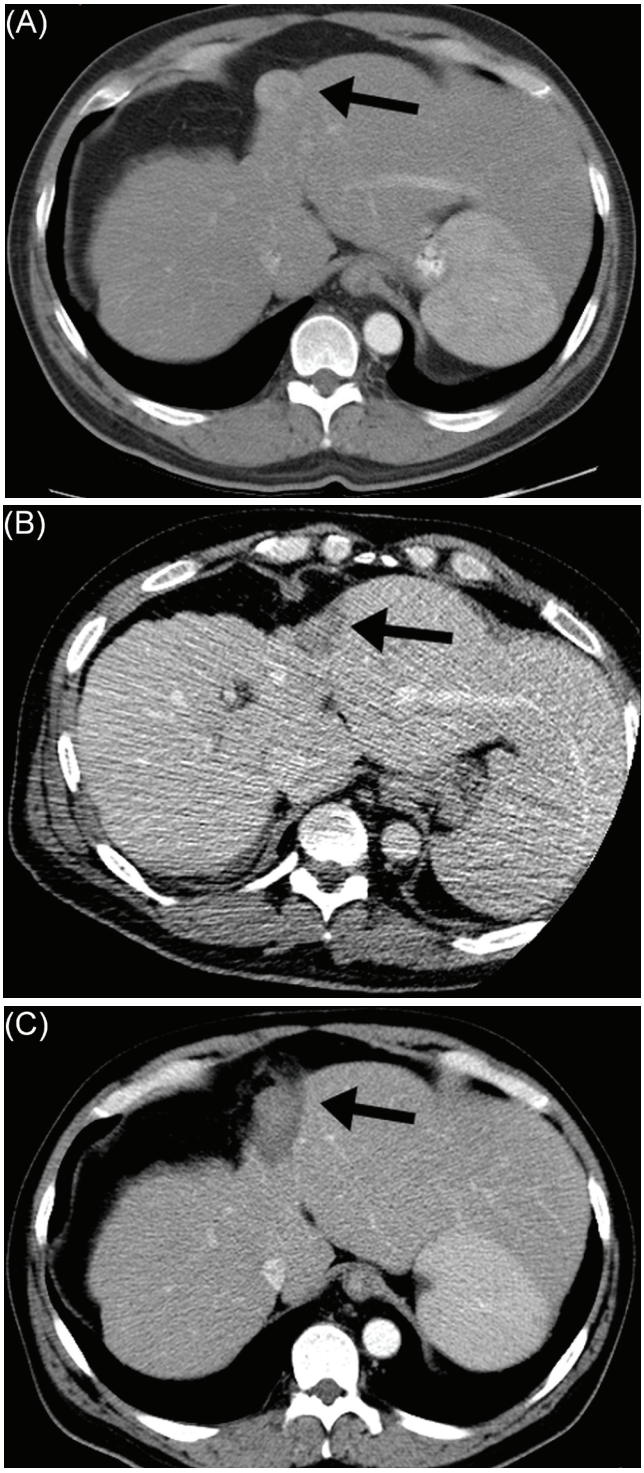

FIGURE 2 Arterial-phase enhanced computed tomography imaging of the liver at similar levels demonstrates the enhancing nodule (arrows) (A) 10 days before treatment, (B) minutes after treatment, and (C) 1 month after treatment with radiofrequency ablation and heat-deployed liposomal doxorubicin.

3. DISCUSSION

Tumour size greater than 3 cm is an important risk factor for local recurrence of HCC after RFA[3]. This risk is likely attributable in part to untreated or unvisualized microscopic disease. Combined therapy takes advantage of the fact that the ablation zone margin is heated to the exact temperature required to release the drug[4]. Timing of the simultaneous delivery of RFA during LTLD infusion is based on preclinical data

suggesting that LTLD is most effective when delivered during hyperthermia[8]. This timing also maximizes the drug delivered (roughly correlated with the area under the curve on the pharmacokinetic graph)[6].

Since completion of the phase I trial, a randomized phase III study comparing RFA plus drug with RFA plus placebo for HCC (search for NCT00617981 at http://clinicaltrials.gov/) has completed accrual, and data are being evaluated. The maximum tolerated dose of LTLD is 50 mg/m^2, which is the standard dose being evaluated in current studies[6].

At 1 month of follow-up in our patient, the maximum axial ablated devascularized zone had increased in size to 53×29 mm [Figure 2(C)] compared with the 34×25 mm seen on the corresponding slice immediately post procedure [Figure 2(B)]. These findings are not typical for RFA. In fact, in RFA alone (without LTLD), the size of the RFA zone decreases with time. In one study, mean lesion volumes measured by summation of areas decreased by 21% at 1 month after RFA[9]. Although the mechanism of this atypical increase in ablation diameter in the weeks post ablation is unclear, theoretical hypotheses include ongoing cytotoxic chemotherapeutic effect, inhibition of adjacent hepatocyte hypertrophy caused by local chemotherapy, or altered atrophy of necrotic cells.

The 2010 American Association for the Study of Liver Diseases guidelines for HCC screening recommend that, based on growth rates of HCC, ultrasonography screening should be performed every 6 months[10]. Although ultrasonography is highly specific, its low estimated sensitivity (approximately 60%) implies that many cases remain undiagnosed[11]. Despite the higher sensitivity of CT or magnetic resonance imaging, imaging costs and the radiation exposure of repeated CT imaging are prohibitive in establishing those modalities as widespread screening techniques.

Although the original lesion was successfully treated, a second tumour (in a different anatomic location) would have remained undiagnosed if not incidentally detected after transplantation. That finding highlights the imperfect nature of even the most sensitive imaging techniques and might explain why alpha fetoprotein levels in our patient were unchanged by the ablation. They were within normal limits before (8.4 ng/mL) and after (9.9 ng/mL) ablation, but markedly decreased to 2.2 ng/mL after transplantation and removal of the second tumour. All local therapies—such as RFA and surgical resection—have fundamental limitations because they do not address the underlying disease and risk factors (such as hepatitis, alcohol use, and cirrhosis). Radiofrequency ablation can be a bridge to transplantation, but the Milan criteria for transplantation establish a cut-off of 5 cm for a single lesion, in contrast with what many accept as a maximum size of 3 cm for RFA alone[12]. Combining RFA with chemotherapy might be a way that this difference can be addressed for tumours larger than 3 cm. A HCC of that kind showed complete necrosis when RFA was combined with intravenous heat-deployed liposomal doxorubicin therapy, with pathology confirmation at transplantation.

4. ACKNOWLEDGMENTS

The work discussed here is supported in part by the U.S. Center for Interventional Oncology, the U.S. National Cancer Institute, and the Intramural Research Program of the U.S. National Institutes of Health (NIH). The NIH and Celsion Corporation have a cooperative research and development agreement (search for NCT00093444 at http://clinicaltrials.gov/, grant no. ZIA BC 011242-03CCRO). The research was made possible through the NIH Medical Research Scholars Program, a public–private partnership supported jointly by the NIH and by generous contributions to the Foundation for the NIH from Pfizer, The Leona M. and Harry B. Helmsley Charitable Trust, the Howard Hughes Medical Institute, and other private donors. For more information, please visit the Foundation's Web site at http://www.fnih.org/work/programs-development/medical-research-scholars-program).

5. DISCLAIMER

The content of this publication does not necessarily reflect the views or policies of the U.S. Department of Health and Human Services, and mention of trade names, commercial products, or organizations does not imply endorsement by the U.S. Government.

6. CONFLICT OF INTEREST DISCLOSURES

The National Institutes of Health and Celsion Corporation have a cooperative research and development agreement. CWH, SKL, and BJW have no other disclosures.

7. REFERENCES

1. Petrowsky H, Busuttil RW. Resection or ablation of small hepatocellular carcinoma: what is the better treatment? *J Hepatol* 2008;49:502–4.
2. Cho YK, Kim JK, Kim MY, Rhim H, Han JK. Systematic review of randomized trials for hepatocellular carcinoma treated with percutaneous ablation therapies. *Hepatology* 2009;49:453–9.
3. Mulier S, Ni Y, Jamart J, Ruers T, Marchal G, Michel L. Local recurrence after hepatic radiofrequency coagulation: multivariate meta-analysis and review of contributing factors. *Ann Surg* 2005;242:158–71.
4. Gasselhuber A, Dreher MR, Negussie A, Wood BJ, Rattay F, Haemmerich D. Mathematical spatio-temporal model of drug delivery from low temperature sensitive liposomes during radiofrequency tumour ablation. *Int J Hyperthermia* 2010;26:499–513.

5. Ranjan A, Jacobs GC, Woods DL, *et al.* Image-guided drug delivery with magnetic resonance guided high intensity focused ultrasound and temperature sensitive liposomes in a rabbit Vx2 tumor model. *J Control Release* 2012;158:487–94.
6. Wood BJ, Poon RT, Locklin JK, *et al.* Phase I study of heat-deployed liposomal doxorubicin during radiofrequency ablation for hepatic malignancies. *J Vasc Interv Radiol* 2012;23:248–55.e7.
7. Berber E, Siperstein AE. Perioperative outcome after laparoscopic radiofrequency ablation of liver tumors: an analysis of 521 cases. *Surg Endosc* 2007;21:613–18.
8. Ponce AM, Viglianti BL, Yu D, *et al.* Magnetic resonance imaging of temperature-sensitive liposome release: drug dose painting and antitumor effects. *J Natl Cancer Inst* 2007;99:53–63.
9. Lim HK, Choi D, Lee WJ, *et al.* Hepatocellular carcinoma treated with percutaneous radio-frequency ablation: evaluation with follow-up multiphase helical CT. *Radiology* 2001;221:447–54.
10. Bruix J, Sherman M on behalf of the American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. *Hepatology* 2011;53:1020–2.
11. Colli A, Fraquelli M, Casazza G, *et al.* Accuracy of ultrasonography, spiral CT, magnetic resonance, and alpha-fetoprotein in diagnosing hepatocellular carcinoma: a systematic review. *Am J Gastroenterol* 2006;101:513–23.
12. Lu DS, Yu NC, Raman SS, *et al.* Percutaneous radiofrequency ablation of hepatocellular carcinoma as a bridge to liver transplantation. *Hepatology* 2005;41:1130–7.

Correspondence to: Bradford J. Wood, 9000 Rockville Pike, Bethesda, Maryland 20892 U.S.A.
E-mail: bwood@cc.nih.gov

* Center for Interventional Oncology, Radiology and Imaging Sciences, National Institutes of Health Clinical Center, Bethesda, MD, U.S.A.
† Lerner College of Medicine, Cleveland Clinic, Cleveland, OH, U.S.A.
‡ Montefiore–Einstein Center for Cancer Care, Department of Surgery, Albert Einstein College of Medicine, Bronx, NY, U.S.A.
§ National Cancer Institute, National Institutes of Health, Bethesda, MD, U.S.A.