CLINICAL STUDY

Combination of Neoadjuvant Transcatheter Arterial Chemoembolization and Orthotopic Liver Transplantation for the Treatment of Cirrhotomimetic Hepatocellular Carcinoma

Peiman Habibollahi, MD, Sara P. Shamchi, MD, Rashmi Tondon, MD, Brett L. Ecker, MD, Terence P. Gade, MD, PhD, Stephen Hunt, MD, PhD, Michael C. Soulen, MD, Emma E. Furth, MD, Matthew H. Levine, MD, PhD, and Gregory Nadolski, MD

ABSTRACT

Purpose: To examine differences in outcome and response of cirrhotomimetic (CMM) hepatocellular carcinoma (HCC) to a combination of bridging transcatheter arterial chemoembolization and orthotopic liver transplantation (OLT) compared with non-CMM HCC.

Materials and Methods: All patients with pathologically proven CMM HCC who underwent bridging transcatheter arterial chemoembolization before OLT between 2007 and 2013 (n = 23) were retrospectively compared with a control group of patients with pathologically proven non-CMM HCC (n = 46).

Results: There were 29 tumors in the CMM HCC group and 64 tumors in the non-CMM group identified and treated. Objective response rate on MR imaging at 1 and 3 months after transcatheter arterial chemoembolization for CMM HCC tumors (including patients with complete and partial response) was 93.1% and 86.4% compared with 85.2% and 93.2% for non-CMM tumors without statistically significant difference ($P = .54$ and $P = .09$, respectively). Pathologic study of liver explants showed complete tumor necrosis in 62.3% of non-CMM tumors (38/61) compared with 10.3% of CMM tumors (3/29) ($P < .0001$). Overall 2-year survival after transcatheter arterial chemoembolization and OLT was significantly lower for patients with CMM HCC compared with patients non-CMM HCC (65.2% vs 87%, $P = .03$). Patients with CMM HCC with extranodular tumor extension involving > 50% of liver parenchyma had worse survival with mean 2-year survival of 402 days ± 102 vs 656 days ± 39 for the remaining patients with CMM HCC ($P = .02$).

Conclusions: Despite similar early imaging response rates, CMM HCC tumors had markedly lower rates of complete pathologic necrosis on liver explants and were associated with reduced survival after OLT compared with conventional HCCs.

ABBREVIATIONS

CMM = cirrhotomimetic, HCC = hepatocellular carcinoma, OLT = orthotopic liver transplantation

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related mortality worldwide (1). Regarding pathologic characteristics and growth pattern, HCC is divided into several forms. Cirrhotomimetic (CMM) HCC is a rare subtype characterized by small tumor nodules spreading and interdigitating within the cirrhotic liver parenchyma (2). CMM HCC has been reported in 7%–20% of all liver explants for HCC (2–6) and behaves more

From the Penn Image Guided Interventions Laboratory (P.H., T.P.G., S.H., G.N.), Department of Radiology (P.H., S.P.S., M.C.S., G.N.), Department of Pathology (R.T., E.E.F.), and Division of Transplant Surgery (B.L.E., M.H.L.), Department of Surgery, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA, 19104. Received March 10, 2017; final revision received August 30, 2017; accepted September 12, 2017. **Address correspondence to** G.N.; E-mail: Gregory.Nadolski@uphs.upenn.edu

M.C.S. receives personal fees from Guerbet (Villepinte, France), Merit Medical Systems, Inc (South Jordan, Utah), Sirtex Medical Ltd (North Sydney, Australia), Terumo Medical Corp (Somerset, New Jersey), and Bayer AG (Berlin, Germany), and grants from Guerbet and BTG International (London, United Kingdom). M.H.L. receives grants from the US Department of Defense (Bethesda, Maryland) and Pfizer (New York, New York). G.N. receives grants from Guerbet, Teleflex Medical (Limerick, Pennsylvania), and Bard (Murray Hill, New Jersey) and personal fees from Teleflex Medical. None of the other authors have identified a conflict of interest.

From the SIR 2016 Annual Scientific Meeting.

https://doi.org/10.1016/j.jvir.2017.09.008

aggressively than other types of HCC, as demonstrated in a study in which patients with non–clear cell histology or CMM tumor cells involving > 50% of liver volume were found to have a markedly lower recurrence-free survival at 3 and 5 years (2). Current medical literature regarding imaging and treatment of CMM HCC is limited (7). Using currently available imaging technology, making the diagnosis of CMM HCC is challenging, and in some patients, the diagnosis is not made until after pathologic evaluation of the explanted liver following orthotopic liver transplantation (OLT) (2). The present study retrospectively evaluated patients undergoing bridging transcatheter arterial chemoembolization followed by OLT who were found to have pathologically proven CMM HCC on liver explants and examined differences in imaging response, pathologic necrosis, and short-term survival compared with patients without CMM HCC.

MATERIALS AND METHODS

Study Population and Clinical Data

Institutional review board approval and waiver of informed consent were obtained. A comprehensive search was performed of the electronic medical records system between January 2007 and March 2014 for all patients who underwent OLT for HCC. All consecutive patients with primary liver explant pathology report stating CMM growth pattern who underwent bridging transcatheter arterial chemoembolization before OLT were included (n = 31). All patients had HCC identified before OLT based on the American Association for the Study of Liver Diseases guidelines (8). Patients were reviewed by the institutional multidisciplinary liver tumor board. Transcatheter arterial chemoembolization was considered for patients listed for OLT with Model for End-Stage Liver Disease exception points and anticipated wait-list time > 6 months as determined by institutional multidisciplinary liver tumor board and liver transplant selection committee.

The CMM HCC group included 23 patients with 29 CMM tumors treated with transcatheter arterial chemoembolization (Fig 1). A control group included 46 patients with 65 non-CMM HCC tumors. After subject identification, patient characteristics, including age, sex, primary diagnosis leading to HCC, dates of transcatheter arterial chemoembolization before transplantation and OLT, survival data, and, if applicable, cause of death, were recorded from the electronic medical record. Model for End-Stage Liver Disease scores at the time of listing and serum alpha fetoprotein values were also recorded. No significant difference was seen between the 2 groups in terms of age, sex, etiology, and tumor distribution and number ($P > .05$). Regarding time to OLT from the first transcatheter arterial chemoembolization treatment, the 2 groups were not significantly different (300 d ± 159 for CMM HCC group vs 250 d ± 264 for non-CMM HCC group, independent t test, $P = .41$). None of the patients received any other form of systemic therapy during the study period, and transcatheter arterial chemoembolization was the only form of locoregional therapy in the study population. Table 1 summarizes the baseline characteristics of the patients.

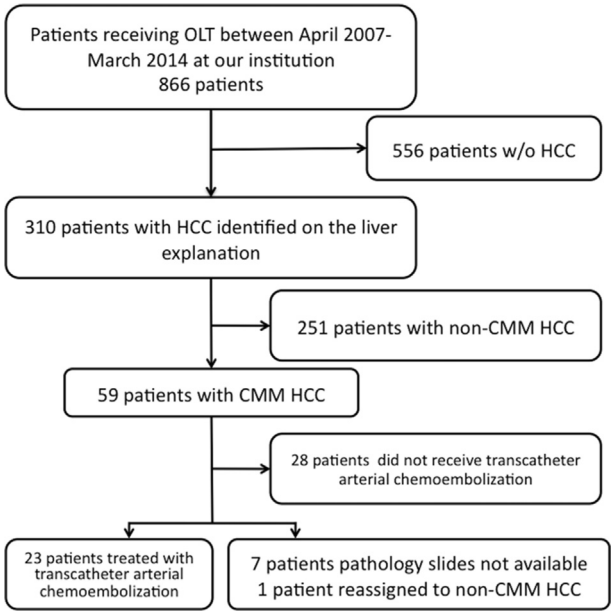

Figure 1. Flowchart of selection of the study population.

To confirm the presence of CMM HCC and characterize specific pathologic features of CMM HCC, a secondary pathology review was performed by a board-certified pathologist and confirmed by a second pathologist with 27 years of experience in the field of hepatopathology. On secondary pathology review, 8 patients were excluded from the CMM HCC group. In 7 patients, liver explant slides were not available. In 1 patient, HCC was characterized as non-CMM in the secondary review. In the remaining 23 patients, 3 patients had coexisting non-CMM HCC tumors in addition to CMM tumors. These 5 tumors (3 tumors in 1 patient and 1 tumor in each of the other 2 patients) were excluded from tumor-specific analysis comparing CMM with non-CMM (imaging response and pathologic necrosis).

Imaging and Bridging Locoregional Therapy

Diagnosis of HCC was made based on characteristic imaging findings on contrast-enhanced multiphase magnetic resonance (MR) imaging, contrast-enhanced multiphase computed tomography, or liver biopsy in accordance with American Association for the Study of Liver Diseases guidelines (8). An institutional quality assurance database (HI-IQ; ConexSys, Lincoln, Rhode Island) and the electronic medical record were reviewed for transcatheter arterial chemoembolization received by the patients. Number, size, and largest diameter of the enhancing portion of HCC tumors on MR imaging before transcatheter arterial chemoembolization were recorded. Response to treatment on follow-up MR imaging