CLINICAL STUDY

Efficacy and Nontarget Effects of Transarterial Chemoembolization in Bridging of HCC Patients to Liver Transplantation: A Histopathologic Study

Ulrike Stampfl, MD, Justo Lorenzo Bermejo, PhD, Christof M. Sommer, MD, Katrin Hoffmann, MD, Karl Heinz Weiss, MD, Peter Schirmacher, MD, Peter Schemmer, MD, Hans-Ulrich Kauczor, MD, Götz M. Richter, MD, Boris A. Radeleff, MD, and Thomas Longerich, MD

ABSTRACT

Purpose: To histologically evaluate the efficacy and nontarget effects induced by transarterial chemoembolization as a "bridge" treatment of hepatocellular carcinoma (HCC) before liver transplantation (LT) and its relation to patient survival.

Materials and Methods: Between October 2003 and January 2011, 51 patients with HCC underwent LT after chemoembolization with iodized oil, small spherical particles, and carboplatin. The decision for LT was made according to national guidelines. The efficacy and nontarget effects of chemoembolization were determined histologically in explanted livers, and their impact on patients' survival after LT was analyzed.

Results: A total of 126 chemoembolization procedures were performed in 51 patients; the median number of procedures per patient was three (range, one to six). The extent of HCC necrosis was less than or equal to 50% in 32% of treated HCCs, more than 50% and less than or equal to 90% in 17%, and more than 90%–99% in 14%; 38% showed complete necrosis of the lesion. The most common nontarget effects were focal necrosis of the liver parenchyma adjacent to the embolized HCC nodule (28%), intralesional (micro)abscess (26%), intralesional hemorrhage (22%), and peritumoral bile duct necrosis (12%). Based on histopathologic examination, 35% of patients had HCC that did not meet Milan criteria. None of these findings was significantly associated with patient survival after LT.

Conclusions: Transarterial chemoembolization induces histopathologically confirmed HCC necrosis with a high degree of efficacy, but histologically proven complete HCC necrosis was not predictive of survival in this cohort of patients. Although histopathologic examination revealed (clinically relevant) nontarget effects in a subset of patients, they did not impair survival.

ABBREVIATIONS

CSS = cancer-specific survival, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, LT = liver transplantation, UCSF = University of California, San Francisco, UICC = Union for International Cancer Control

From the Departments of Diagnostic and Interventional Radiology (U.S., C.M.S., H.U.K., G.M.R., B.A.R.), General and Transplant Surgery (K.H., P. Schemmer), and Gastroenterology (K.H.W.), Institute of Medical Biometry and Informatics (J.L.B.), Liver Cancer Center Heidelberg (K.H.W., P. Schirmacher, P. Schemmer), and Institute of Pathology (P. Schirmacher, T.L.), University Hospital Heidelberg, Im Neuenheimer Feld 110, 69120 Heidelberg, Germany; and Department of Diagnostic and Interventional Radiology (C.M.S., G.M.R.), Katharinenhospital Stuttgart, Stuttgart, Germany. Received October 7, 2013; final revision received and accepted March 5, 2014. **Address correspondence to** U.S.; E-mail: ulrike.stampfl@med.uni-heidelberg.de

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Hepatocellular carcinoma (HCC) is one of the most frequent cancers worldwide, with well characterized underlying etiologies resulting in liver cirrhosis as the main risk factor (1). Liver transplantation (LT) is the best therapeutic option for patients with HCC because it not only removes the tumor, but may also cure the underlying chronic liver disease. The interval between HCC diagnosis and LT is an important prognostic factor, as dropout rates from the waiting list as a result of tumor progression increase in a time-dependent manner (2). In this context, locoregional therapies, transarterial chemoembolization in particular, play an important role to control tumor growth (3,4). In the single-center study reported here, we retrospectively analyzed the explanted livers of 51 patients with HCC who underwent LT after

"bridge" therapy with transarterial chemoembolization to determine factors that correlated with patient survival. The primary study endpoint was the efficacy of transarterial chemoembolization as determined by histopathologic evaluation of tumor necrosis. The secondary endpoints were nontarget effects as determined by histopathologic examination and their potential influence on patient survival after LT.

MATERIALS AND METHODS

Patients

Institutional review board approval was obtained to conduct this retrospective study. Demographic, procedural, and follow-up data of 51 consecutive patients (47 men and four women; mean age, 56 y ± 7; median age, 56 y; age range, 45–68 y) diagnosed with HCC according to European Association for the Study of the Liver/European Organisation for Research and Treatment of Cancer clinical practice guidelines (5) who underwent LT after at least one chemoembolization procedure between October 2003 and January 2011 were reviewed. The histopathologic findings of the explanted livers were reevaluated by two liver pathologists (T.L., P.S.). Magnetic resonance (MR) imaging with a liver-specific contrast agent (Primovist; Bayer, Leverkusen, Germany) was obtained in all patients before the first chemoembolization procedure. The treatment schedule included three chemoembolization procedures with an interval of 4 weeks between procedures. Before every chemoembolization procedure, follow-up MR imaging with non–liver-specific contrast agent was performed to monitor the tumor response. Three months after each treatment cycle, MR imaging with liver-specific contrast agent was performed. Patients with residual tumor underwent another treatment cycle. Staging was performed according to Union for International Cancer Control (UICC) criteria. In addition, it was evaluated whether patients' disease fulfilled the Milan criteria (6) by radiologic imaging and histopathologic analyses of explanted livers. The decision for transplantation was made in a multidisciplinary tumor board according to national guidelines based on the Milan criteria and European Association for the Study of the Liver guidelines, and allocation occurred via the Eurotransplant system (5,6).

Transarterial Chemoembolization

Written informed consent was obtained from all patients before chemoembolization. A microcatheter was used in all patients. In principle, a superselective microcatheter position was intended for embolization. Only if no superselective microcatheter position was feasible because of the anatomic conditions or distribution of the HCC nodules, a lobar embolization was performed. Chemoembolization was performed in a "sandwich technique" as follows. First, iodized oil (Ethiodol; Guerbet, Roissy, France) was injected to obtain initial reduction of blood flow. Then, small microspheres (Embosphere; Merit Medical, Maastricht, The Netherlands; or Embozene; CeloNova BioSciences, San Antonio, Texas) were prepared according to the manufacturers' recommendation and injected to further reduce the tumor perfusion. Twenty-two patients were treated solely with Embosphere microspheres, 23 patients received solely Embozene microspheres, and six patients were treated with both types of embolic agents. Overall, 55 chemoembolization procedures were performed with 40–120-μm Embosphere particles, two with 100–300-μm Embosphere particles, and one with 300–500-μm Embosphere particles. Embosphere particles of two different sizes were used in two of these procedures. A total of 25 chemoembolization procedures were performed with 40-μm Embozene particles, 41 with 100-μm Embozene particles, and two with 250-μm Embozene particles. Injection of microspheres was followed by the administration of 200 mg carboplatin, and additional microspheres and iodized oil were then injected. The endpoint for lobar and superselective embolization was stasis of flow distal to the tip of the microcatheter.

Histopathology

After formalin fixation, explanted livers were dissected in 0.5-cm sections to identify focal liver lesions. All visible tumor nodules were sampled for histologic analysis in at least the maximal diameter of the lesion. In macroscopically necrotic lesions, any potentially viable tissue was forwarded for histologic assessment. After paraffin-embedding, 3-μm sections were prepared, and histologic assessment of chemoembolization efficacy and related nontarget effects was based on hematoxylin and eosin–stained slides. For the evaluation of underlying liver disease, periodic acid–Schiff after diastase digestion, Perl stain, and a modified Gomori stain were routinely performed from the surrounding, nonneoplastic liver parenchyma of both liver lobes.

The following histologic parameters were assessed semiquantitatively: grading (no remaining viable tumor [Gx], well differentiated [G1], moderately differentiated [G2], poorly differentiated [G3]), UICC staging, tumor size ($\leq$ 3 cm, $>$ 3–5 cm, $>$ 5 cm), HCC necrosis ($\leq$ 50%, 50%–90%, $>$ 90%–99%, no viable tumor), and particles in surrounding liver (none, discrete, prominent).

The following parameters were evaluated qualitatively: whether HCC fulfilled Milan and University of California, San Francisco (UCSF), criteria (size of largest nodule and number of HCC nodules identified during pathologic workup); presence of intralesional (micro)abscess; biloma; intralesional hemorrhage; focal necrosis of surrounding nonneoplastic liver parenchyma; inflammatory foreign-body reaction within the embolized