Prospective Evaluation of Patients with Early-/Intermediate-stage Hepatocellular Carcinoma with Disease Progression Following Arterial Locoregional Therapy: Candidacy for Systemic Treatment or Clinical Trials

Khairuddin Memon, MD, Laura Kulik, MD, Robert J. Lewandowski, MD, Ramona Gupta, MD, Robert K. Ryu, MD, Frank H. Miller, MD, Michael Vouche, MD, Rohi Atassi, DDS, Daniel Ganger, MD, Mary F. Mulcahy, MD, and Riad Salem, MD, MBA

ABSTRACT

Purpose: During the course of cancer treatment, patients whose disease progresses despite therapy are offered alternative options. Similarly, patients with hepatocellular carcinoma (HCC) whose disease progresses following arterial locoregional therapies (LRTs) cross over to undergo systemic therapies or participate in clinical trials. Per current guidelines, patients must meet inclusion criteria (most importantly Child–Pugh class A status) to qualify for systemic options. The present study analyzed the candidacy for systemic agents or clinical trials of patients whose disease progresses despite LRTs.

Materials and Methods: A total of 245 patients with HCC were treated with LRTs (chemoembolization, n = 123; yttrium-90 [^{90}Y] radioembolization, n = 122) as part of a previously published comparative effectiveness study; 96 patients exhibiting disease progression were followed prospectively. Modes of progression (cancer stage, Child–Pugh class) were analyzed to determine candidacy for systemic therapy or clinical trials, as well as assess ultimate treatment(s) received.

Results: Among the 96 patients with disease progression, 52% and 48% had Child–Pugh class A and class B/C disease, respectively, thereby substantially limiting the latter group's eligibility for systemic therapy and/or clinical trials. Of those whose disease progressed who had advanced-stage HCC, 63% had Child–Pugh class B/C disease. By size and necrosis criteria, the local disease progression rate was higher with chemoembolization than with ^{90}Y radioembolization ($P = .006$ and $P = .016$, respectively). Of the 96 patients with disease progression, only 13 (13%) ultimately received systemic agents or entered clinical trials.

Conclusions: Most patients with advanced HCC that progresses following LRTs were not candidates for clinical trials or systemic agents. There is a need for future research efforts directed at treatment options or novel trial designs that will permit inclusion of patients with progressive liver disease and suboptimal liver function.

ABBREVIATIONS

BCLC = Barcelona Clinic Liver Cancer, EASL = European Association for the Study of the Liver, HCC = hepatocellular carcinoma, LRT = locoregional therapy, NCT = National Clinical Trials, PD = progressive disease, TTP = time to progression, UNOS = United Network for Organ Sharing, WHO = World Health Organization

From the Department of Radiology, Section of Interventional Radiology, and Division of Interventional Oncology (K.M., R.J.L., R.G., R.K.R., F.H.M., M.V., R.A., R.S.), and Department of Medicine, Division of Hematology and Oncology (M.F.M., R.S.), Robert H. Lurie Comprehensive Cancer Center; and Department of Medicine, Division of Hepatology (L.K., D.G.), Northwestern University, 676 N. St. Clair, Suite 800, Chicago, IL 60611. Recieved October 22, 2012; final revision received December 21, 2012; accepted December 29, 2012. **Address correspondence to** R.S.; E-mail: r-salem@northwestern.edu

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Tables E1 and E2 are available online at *www.jvir.org*.

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In most systemic cancers (eg, breast, colon), patients whose disease progresses cross over to undergo another treatment or participate in clinical trials. Although the same is true for hepatocellular carcinoma (HCC), the eligibility of these patients for other (systemic) therapies is often limited by background cirrhosis and liver dysfunction. Historically, the role of systemic agents in this setting was limited until two randomized studies demonstrated a survival benefit with sorafenib in advanced HCC (1,2). This led a consensus panel to recommend sorafenib as the standard of care for patients whose disease progresses after locoregional therapy (LRT) (3,4). Although both of these studies enrolled patients with advanced HCC that had progressed with local therapies, Child–Pugh class A disease status was a necessary inclusion criterion. This was important to minimize the possibility of background liver dysfunction masking the potential effectiveness of the test agent (at the time), sorafenib. As a result, guidelines now suggest clinical trials with systemic agents should be performed in patients with Child–Pugh class A disease (3).

The exact reasons for trial ineligibility in advanced HCC are poorly documented in the literature. As recently demonstrated in a similar analysis of a population with more advanced disease (5), they are predominantly related to liver (dys)function. Given this background, our primary aim in the present investigation was to study the clinical status (Child–Pugh class, cancer stage) of 96 patients with early-/intermediate-stage HCC (per Barcelona Clinic Liver Cancer [BCLC] staging) that showed progression following intraarterial LRTs (6). We strictly adhered to the inclusion criteria from the seminal sorafenib studies and defined a candidate for treatment with a systemic agent and/or clinical trial participation as a patient whose disease progressed despite LRTs and showed vascular invasion or extrahepatic metastases and Child–Pugh class A disease (1,2). Although we recognize that not all patients had Child–Pugh class A disease at baseline, the intent was to follow patients in a manner paralleling clinical practice and apply LRTs in patients with Child–Pugh class A disease and select patients with Child–Pugh class B disease (per BCLC staging), and subsequently assess feasibility of systemic agents at progression. Secondary aims included analyzing (i) long-term effects of LRTs on liver function at progression, (ii) radiographic pattern of HCC progression, and (iii) follow-up of patients to further characterize their eventual postprogression clinical course.

MATERIALS AND METHODS

This is a prospective follow-up to a published 245-patient comparative effectiveness study of chemoembolization and radioembolization (6). In the initial study, radioembolization was associated with fewer hepatic adverse events ($P = .004$), similar survival times ($P = .7803$), and longer time to progression (TTP; $P = .046$). At the time of data analysis (median follow-up, 32.6 and 22.7 mo for chemoembolization and radioembolization, respectively), patients exhibiting progression on imaging were identified and followed prospectively. To gain insight into the characteristics of patients with progressing disease, we analyzed variables at the time of progression deemed of clinical interest, including Child–Pugh status, United Network for Organ Sharing (UNOS) stage, and imaging findings resulting in the designation of progressive disease (PD; local progression, new lesions, metastases, vascular invasion). All postprogression systemic or local treatments, as well as enrollment in clinical trials, were documented until the patient's death.

This resulted in the identification of 96 patients with HCC that progressed after intraarterial LRTs (chemoembolization, n = 54; yttrium-90 [^{90}Y] radioembolization, n = 42); this constitutes the present study population (**Figure**). Institutionally, as part of our research mission, we considered these patients for clinical trials with systemic agents. This study was approved by the Northwestern University Institutional Review Board and is Health Insurance Portability and Accountability Act compliant.

Evaluation and Staging

Diagnostic criteria for HCC included biopsy or radiographic findings as defined by published guidelines (3). Baseline staging (Child–Pugh liver function, UNOS tumor/node/metastasis classification of tumor size and number, and BCLC liver function, tumor size/number, and symptoms) was performed (**Table E1**; available online at *www.jvir.org*) (3). Patients were categorized as having cirrhosis if they exhibited nodular liver margin, splenomegaly, and/or varices. Patients were deemed to have portal hypertension in the presence of varices, splenomegaly, and/or thrombocytopenia (ie, platelet count $<100{,}000/\mu L$).

LRTs

Chemoembolization was performed with the use of 30 mg mitomycin, 30 mg doxorubicin, and 100 mg cisplatin mixed with Lipiodol and embolic particles (7). Radioembolization with ^{90}Y was performed with glass microspheres (Nordion, Ottawa, Ontario, Canada) per previously described standardized treatment protocols (8–10).

Analysis of Progression

After treatment with LRTs, patients were scanned by using cross-sectional imaging 1 month following treatment and at scheduled 2–3-month intervals. Liver function tests obtained coincided with imaging. All scans were analyzed by World Health Organization (WHO) size and European Association for the Study of the Liver (EASL) necrosis criteria (**Table E2**; available online at *www.jvir.org*) (1,11–15). For each scan, the different imaging findings of progression were recorded, and observation of any of the following constituted a TTP endpoint: PD per (i) WHO or (ii) EASL criteria, (iii) new tumors, or (iv) development of