CLINICAL STUDY

Locoregional Therapy for Hepatocellular Carcinoma with and without Extrahepatic Spread

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ABSTRACT

Purpose: To evaluate the use of locoregional therapy in patients with hepatocellular carcinoma (HCC) with and without extrahepatic disease (EHD).

Materials and Methods: Patients who underwent locoregional therapy for HCC were identified from institutional databases. Clinicopathologic and treatment characteristics were compared between patients with and without EHD. Survival and progression were assessed using the Kaplan-Meier method, and multivariate analysis was completed.

Results: Of 224 patients, 39 (17%) had radiologic evidence of EHD. Patients without EHD were older than patients with EHD (68.8 y ± 10.1 vs 65.0 y ± 11.7, $P = .04$); underlying liver disease/function and tumor characteristics were not different. Type of locoregional therapy (hepatic artery embolization vs drug-eluting bead transarterial chemoembolization, $P = .12$; radiofrequency ablation + embolization, $P = .07$) was similar. Progression occurred in 75% (169/224) of patients. Progression-free survival (PFS) did not differ between the 2 groups (13 [10.3–15.7] mo EHD vs18 [14.6–21.4] mo no EHD, P = .13). Overall survival (OS) was 13 (4.1–21.9) months and 25 (20.4–29.6) months in the EHD and no EHD groups, respectively ($P = .02$). On multivariate analysis, systemic therapy after locoregional treatment was the only variable independently associated with PFS (hazard ratio [HR] 0.70 [0.49–1.00], $P = .04$); EHD (HR 1.60 [1.02–2.50], $P = .04$) and tumor size (HR 1.77 [1.21–2.58], $P = .003$) were independently associated with worse OS.

Conclusions: Patients with HCC and limited EHD treated with locoregional therapy had worse OS than patients without EHD; PFS was not different. Use of systemic therapy after locoregional therapy was independently associated with improved PFS in this cohort. Further prospective studies of locoregional, systemic, and combination therapies are necessary to improve outcome in these high-risk patients.

ABBREVIATIONS

DEB = drug-eluting bead, EHD = extrahepatic disease, HAE = hepatic artery embolization, HCC = hepatocellular carcinoma, HR = hazard ratio, LN = lymph node, OS = overall survival, PFS = progression-free survival, SHARP = Sorafenib HCC Assessment Randomized Protocol

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Over the past 3 decades, the incidence of hepatocellular carcinoma (HCC) in the United States has nearly tripled. This increase is primarily driven by increased rates of chronic hepatitis C infection and nonalcoholic fatty liver disease (1). Treatment options and prognosis for HCC are contingent on the complex interplay between the degree of underlying liver disease and tumor stage at diagnosis. Despite recommendations for regular HCC screening in high-risk populations by the American Association for the Study of Liver Disease (2), implementation in the United States has been poor with < 20% of eligible patients undergoing routine surveillance (3). Consequently, more than

two-thirds of patients present with advanced disease that is not amenable to curative resection or transplantation, and 5-year survival remains very poor (< 5%) (4).

Patients with Barcelona Clinic Liver Cancer intermediate or advanced HCC are diverse and include patients with locally advanced disease and patients with extrahepatic disease (EHD), decompensated liver disease, or poor functional status (5). The heterogeneity of this cohort, the complicated interaction between tumor burden and liver function, and the concurrent evolution of locoregional and systemic therapies make treatment decisions in this cohort complex, and multidisciplinary evaluation is essential before institution of any form of therapy (6). In patients with intermediate disease confined to the liver, locoregional therapies including hepatic artery embolization (HAE) and transarterial chemoembolization are accepted modes of treatment (7). In 2002, two randomized clinical trials (8,9) showed a survival benefit of transarterial chemoembolization over best supportive care in patients with intermediate HCC. In a meta-analysis by Llovet and Bruix (10) of seven randomized clinical trials of patients with unresectable HCC, embolization was shown to provide a significant survival benefit compared with observation alone. Although transarterial chemoembolization is regarded by some authors as the superior method of embolization, randomized clinical trial data published more recently demonstrated no significant survival difference between transarterial chemoembolization, drug-eluting bead (DEB) transarterial chemoembolization, and bland HAE (11–13). Consequently, the most recently published National Comprehensive Cancer Network consensus guidelines for the treatment of HCC suggest embolization, either bland HAE or transarterial chemoembolization, as the standard of care for patients with intermediate or advanced HCC without extrahepatic spread or main portal vein involvement (14).

In patients with advanced or metastatic disease, embolization therapy is not considered standard of care, and with the advent of sorafenib, primary treatment is often systemic (15,16). Natural history studies of HCC suggest that tumor burden within the liver contributes significantly to hepatic decompensation and death (17,18). One may hypothesize that the use of locoregional therapies to control liver disease may provide a survival benefit even in patients with EHD. To date, no definitive evidence to support or refute the use of locoregional therapy alone or in combination with systemic therapy exists. Given this paucity of evidence, the present study analyzed the use of locoregional therapies, including bland HAE and DEB transarterial chemoembolization, in patients with advanced HCC with and without low-volume EHD to evaluate the impact on disease progression and survival.

MATERIALS AND METHODS

Study Design

This retrospective study was approved via waiver of patient consent obtained from the institutional review board at the study center. All patients who underwent HAE or DEB transarterial chemoembolization for the treatment of HCC between January 1, 2008, and August 1, 2013, were identified from prospectively maintained institutional and service-specific databases. Only patients in whom the procedure was their first locoregional treatment were included. Diagnosis of HCC was noninvasive and based on the presence of characteristic radiographic findings (2). In a small number of patients in whom radiographic features were inconsistent or equivocal, tissue diagnosis was required. Patients with Child-Pugh class A or B liver function and intermediate or advanced stage HCC, as defined by the Barcelona Clinic Liver Cancer staging system (5), were reviewed at a multidisciplinary hepatobiliary consensus conference. By definition, these patients were not candidates for surgery or transplantation. All patients in whom HCC was limited to the liver were considered for transarterial locoregional therapy. Patients with limited EHD, defined as solitary bone/adrenal/soft tissue metastasis, scattered small lung nodules, or regional nodal disease, were judged as having "liver-dominant" disease and were considered for locoregional therapy.

Between January 2008 and August 2013, 607 patients underwent 1,205 locoregional procedures. Of the 607 patients, 264 had a primary diagnosis of HCC, and the medical records of these patients were reviewed. There were 40 patients who had undergone locoregional treatment for HCC before the study period, and these patients were excluded; 224 patients were deemed appropriate and included in final analysis. Of study patients, 177 (79%) were men, and the mean age was 68.1 years ± 10.4. At the time of initial presentation, 39 (17.4%) patients had evidence of EHD and 185 (82.6%) did not. **Table 1** outlines baseline demographic characteristics for the group as a whole and is stratified further by the presence or absence of EHD. Patients without EHD at presentation were significantly older than patients with EHD (68.8 y ± 10.1 vs 65.0 y ± 11.7, $P = .04$). Previous treatment was defined as any HCC-directed surgical or systemic therapy received before the initial locoregional treatment. The presence and type of underlying liver disease ($P = .28$), Child-Pugh classification ($P = .59$), and use of previous treatment ($P = .11$) were not different between groups.

Data Collection and Definitions

Target lesion was defined radiographically as the largest measureable lesion in any dimension on initial imaging. EHD was characterized radiographically and recorded according to the anatomic site. As previously reported, lymph node (LN) involvement by tumor can be difficult