CLINICAL STUDY

Transarterial Chemoembolization within First 3 Months of Sorafenib Initiation Improves Overall Survival in Hepatocellular Carcinoma: A Retrospective, Multi-Institutional Study with Propensity Matching

David E. Kaplan, MD, MSc, Rajni Mehta, MPH, Kathryn D'Addeo, BS, Terence P. Gade, MD, PhD, and Tamar H. Taddei, MD

ABSTRACT

Purpose: The impact of transarterial chemoembolization after initiation of sorafenib (SOR) has not been prospectively compared with SOR alone in unresectable hepatocellular carcinoma (HCC). The objective of this study was to assess whether SOR + transarterial chemoembolization provides benefit over SOR alone in this setting.

Materials and Methods: A retrospective cohort study with propensity matching using data from patients prescribed SOR for HCC at Veterans Health Administration hospitals from 2007 to 2015. The primary outcome was overall survival from the time of SOR prescription and stratified by receipt of transarterial chemoembolization within 90 days of SOR initiation.

Results: A total of 4,896 patients received SOR for HCC, of whom 232 (4.7%) underwent transarterial chemoembolization within 90 days. Patients receiving transarterial chemoembolization + SOR were highly selected, being younger and with less significant hepatic dysfunction, earlier Barcelona Clinic Liver Cancer stage ($P < .0001$), and fewer tumors with lower rates of macrovascular invasion (MVI) and metastases (all $P < .0001$) than SOR-alone patients. In unadjusted analysis, SOR + transarterial chemoembolization was associated with reduced mortality (hazard ratio [HR] 0.61, 95% confidence interval [CI] 0.53–0.71; $P < .0001$). After propensity matching, SOR + transarterial chemoembolization continued to show significant associations with reduced mortality with HR 0.75 (95% CI 0.62–0.92; $P = .0005$). Subgroup analysis suggests that the addition of transarterial chemoembolization to SOR improves outcomes in most patients, particularly those with Model for End-Stage Liver Disease score <15, platelets >50,000/μL, and >3 tumors with or without macrovascular invasion, without local invasion or metastases.

Conclusions: Patients with unresectable HCC started on systemic therapy with SOR appear to benefit from adjuvant transarterial chemoembolization. Optimal application of multimodal therapy in this setting should be prospectively investigated.

ABBREVIATIONS

BCLC = Barcelona Clinic Liver Cancer, CTP = Child-Turcotte-Pugh, ECOG = Eastern Cooperative Oncology Group, HCC = heptaocellular carcinoma, MVI = macrovascular invasion, SOR = sorafenib

A minority of patients with hepatocellular carcinoma (HCC) present with early-stage disease amenable to initial curative surgical therapy (1). Locoregional palliative ablative and embolic therapies may prolong overall survival in intermediate-stage disease, but most patients with progressive intermediate- or advanced-stage disease are considered for

From the Department of Medicine (D.E.K.), University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania; Corporal Michael J. Crescenz VA Medical Center (D.E.K., T.P.G.), 3900 Woodland Avenue, Bldg 21, Room A422, Philadelphia, PA 19014; Yale University School of Medicine (R.M., K.D., T.H.T.), New Haven, Connecticut; VA Connecticut Healthcare System (R.M., K.D., T.H.T.), West Haven, Connecticut; and Department of Radiology (T.P.G.), University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania. Received May 31, 2017; final revision received and accepted November 14, 2017. **Address correspondence to** D.E.K.; E-mail: dakaplan@mail.med.upenn.edu

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Appendix A and Table E1 are available online at *www.jvir.org*.

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EDITORS' HIGHLIGHTS

- In a VA study of nearly 4,900 HCC patients, most patients with unresectable HCC, including intermediate stages, were treated with the use of sorafenib.
- When transarterial chemoembolization was performed within 90 days of sorafenib initiation, patients experienced lower mortalities.
- The sorafenib + transarterial chemoembolization patients were younger, had better liver function, and had earlier BCLC stages ($P < .0001$) and tumors than sorafenib-alone patients. This benefit was further demonstrated with the use of propensity score matching.
- Combination therapy may warrant large-scale prospective evaluation.

treatment with the use of sorafenib (SOR) only, a multitarget tyrosine kinase inhibitor, which for the past 10 years has been the only first-line Food and Drug Administration (FDA)–approved systemic therapy proven to provide consistent survival benefits (2,3). There has been significant clinical interest in combining locoregional and systemic therapy to optimize outcomes in intermediate- and advanced-stage HCC (**Table E1** [available online at *www.jvir.org*]), most often with the use of SOR as adjuvant therapy for embolotherapy (transarterial chemoembolization) in an effort to improve outcomes when transarterial chemoembolization does not fully sterilize the target lesion(s). When evaluated retrospectively in transarterial chemoembolization-refractory treatment-naïve Barcelona Clinic Liver Cancer (BCLC) stage B and C patients, the majority of data suggests improved time to progression (TTP) and overall survival (OS) with the use of adjuvant SOR compared with transarterial chemoembolization alone (4–9). Although single-arm prospective studies combining either conventional transarterial chemoembolization or doxorubicin-eluting bead transarterial chemoembolization with SOR in Child-Turcotte-Pugh (CTP) A patients with early- through advanced-stage HCC have shown encouraging survival and tolerability, with median OS ranging from 12 to 20 months (10–13), prospective randomized controlled trials comparing transarterial chemoembolization + SOR to transarterial chemoembolization alone have not shown improvements in overall survival (14–17). Nonetheless, meta-analyses of these prospective studies generally suggest that the addition of SOR to TACE does significantly improve TTP (18–23).

In the United States, SOR was approved by the FDA in 2007 for use in unresectable HCC. In addition to advanced-stage HCC, SOR has broadly been used in unresectable early- and intermediate-stage HCC in the US (24), sometimes in stages for which curative therapies could still be considered. For some individuals, transarterial chemoembolization has been applied after SOR initiation (SOR + transarterial chemoembolization) to reduce intrahepatic progression; however, few data support that practice. The impact of SOR + transarterial chemoembolization compared with SOR alone in intermediate- and advanced-stage HCC has been evaluated retrospectively in two small studies (25,26), one of which suggested a reduced risk of death associated with SOR + transarterial chemoembolization, particularly in BCLC B patients (26). The objectives of the present study were to test the hypothesis that SOR + transarterial chemoembolization would be associated with improved overall survival compared with SOR alone in early, immediate, and advanced disease after a clinical decision to initiate systemic therapy had been made, adjusting for baseline covariates associated with receipt of transarterial chemoembolization, and to determine patient subgroups most likely to benefit from the combination therapy.

Table 1. Propensity Models

Variable	Estimate	Std. Error	z	*P* value
(Intercept)	−126.31	65.30	−1.93	.05
Age	−0.02	0.01	−2.62	.009*
CTP score	−0.20	0.07	−2.75	.006*
BCLC stage	−0.37	0.12	−3.18	.001*
Cirrhosis comorbidity score	−0.02	0.04	−0.40	.69
ECOG PS >2	−0.07	0.62	−0.11	.91
MELD score	−0.05	0.02	−2.32	.02
Specialty prescribing	0.08	0.07	1.20	.23
Race/ethnicity	−0.02	0.03	−0.54	.59
Year	0.06	0.03	1.97	.05
Male sex	−1.21	0.43	−2.85	.004*
Sorafenib started at full dose	0.04	0.15	0.28	.78
Macrovascular invasion	−0.22	0.22	−0.99	.32
Metastases present	−0.88	0.30	−2.97	.003*
Local invasion	−0.25	0.40	−0.62	.54
TACE before sorafenib	0.21	0.04	5.07	<.0001*

Note–Null deviance: 1,868.4 on 4,902 degrees of freedom; Residual deviance: 1,726.1 on 4,887 degrees of freedom; 0 observations deleted due to missingness; AIC: 1,758.1.
BCLC = Barcelona Clinic Liver Cancer; CTP = Child-Turcotte-Pugh; MELD = Model for End-Stage Liver Disease; ECOG PS = Eastern Cooperative Oncology Group performance status.
*$P < .05$.

MATERIALS AND METHODS

Identification of Patients, Data Collection

Development of the cohort has been previously described and is detailed in **Appendix A** (available online at *www.jvir.org*) (24,27–34). Briefly, data from all US veterans prescribed SOR from November 16, 2007, to April 15, 2015, were identified from the Veterans Health Administration (VHA) Corporate Data Warehouse (CDW). Manual chart abstraction was used to confirm HCC diagnosis, to identify HCC stage based on imaging closest to the time of SOR initiation, and to estimate Eastern Cooperative Oncology Group (ECOG)