Published in final edited form as:

J Vasc Interv Radiol. 2018 April ; 29(4): 540–549.e4. doi:10.1016/j.jvir.2017.11.033.

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

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.

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 $\pm$ 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

Address correspondence to D.E.K.; dakaplan@mail.med.upenn.edu.

None of the authors have identified a conflict of interest.

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

>50,000/ μ L, 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.

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 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, intermediate, 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.

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) performance status (PS). BCLC stage was calculated based on collected component variables (34).

Definition of Exposure

The exposure of interest was receipt of transarterial chemoembolization within 90 days after SOR initiation. This window was selected based on the assumption that repeated cross-sectional imaging to assess SOR responsiveness would not yet have been performed and therefore transarterial chemoembolization was most likely a planned component of the initial treatment plan. Inclusion of individuals receiving transarterial chemoembolization >90 days after SOR would also introduce immortal time bias. Individuals receiving transarterial chemoembolization >90 days after SOR initiation (4%) were included in the SOR- alone group, simulating an intention-to-treat analysis.

Definition of Outcomes

Our primary outcome of interest was OS, calculated as the time from initiation of SOR to the time of death, which was ascertained with the use of the Veterans Affairs (VA) Vital Status Master File, an aggregate of the main federal mortality databases and previously shown to have a >97% agreement compared with the criterion-standard state death certificate registries (35). All survival data were censored as of December 31, 2015. Total medication days estimates the total cumulative number of days that each patient took SOR, calculated as the sum of all prescription durations.

Statistical Analysis

Univariate analysis was performed with the use of Fisher exact test for dichotomous variables and Student t test or Wilcoxon rank sum test for normal and nonnormal continuous variables, respectively. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated with the use of the Cox proportional hazards model. Propensity matching was used to simulate randomization and stratification that would occur in a prospective trial to test the impact of SOR + transarterial chemoembolization versus SOR alone. Propensity models were constructed with the use of logit models in R and evaluated to balance covariates associated with early transarterial chemoembolization exposure among SOR-treated patients (Table 1). Models included age, CTP score, BCLC stage, cirrhosis comorbidity score, ECOG PS, Model for End-Stage Liver Disease (MELD) score, specialist,

race/ethnicity, year of SOR initiation, sex, SOR starting dose (full vs reduced), previous receipt transarterial chemoembolization, and presence of macrovascular invasion, local invasion, and metastases. Propensity matching was performed with the use of the R Matchit package with nearest-matching methods and a 2:1 control-case ratio without replacement matching exactly on CTP score, BCLC stage, MELD score, presence of metastases, and number of pre-SOR transarterial chemoembolization procedures. Matched cohorts were inspected for balancing of covariates and then used for Cox proportional hazards modeling and Kaplan-Meier methodology to estimate differences in survival and HRs associated with transarterial chemoembolization exposure. Cox proportional hazards models of individual subgroups selected a priori were then generated.

RESULTS

Time Trends, Unadjusted Demographic Data, and Unadjusted Survival

Initial case identification by means of International Classification of Diseases (ICD), 9th Revision, Clinical Modification codes and pharmacy data identified 5,172 patients with SOR prescriptions for HCC. Of these, 176 prescriptions were ordered but never picked up by the patient, in 92 patients the diagnosis of hepatocellular carcinoma could not be substantiated, and 9 received SOR before FDA approval via a clinical trial, yielding 4,896 patients (94.7%) available for analysis. A total of 232 patients underwent SOR + transarterial chemoembolization compared with 4,662 SOR alone (Table 2). The use of transarterial chemoembolization within 90 days after SOR was consistent over the study period with 3.6%–6.0% of patients receiving combined therapy per year of SOR initiation (Fig 1a; $P = .12$ for differences by year). SOR + transarterial chemoembolization patients were of similar age, less often white, more frequently BCLC stage A or B, less likely to have severe comorbidities, less likely to have ECOG PS 2, had lower CTP and MELD scores, had slightly fewer tumor nodules and a trend toward smaller tumor sizes, and were more likely to have SOR prescribed by a hepatologist rather than an oncologist compared with SOR-alone patients.

SOR + transarterial chemoembolization patients were also more likely than SOR-alone patients to have undergone transarterial chemoembolization before SOR, with a median of 1 (interquartile range [IQR] 0–2) compared with 0 (IQR 0–0) transarterial chemoembolization before initiating SOR; fewer than 4% of patients in either group underwent >3 transarterial chemoembolization procedures before SOR. SOR + transarterial chemoembolization patients received an average of 1.5 transarterial chemoembolization procedures while exposed to SOR, and 4% of SOR patients received transarterial chemoembolization >90 days into SOR treatment (data not presented); 40% of SOR transarterial chemoembolization patients and 4% of SOR-alone patients received transarterial chemoembolization after discontinuing SOR.

Starting and average doses for SOR were similar across groups. SOR + transarterial chemoembolization patients were more likely than SOR-alone patients to discontinue SOR because of adverse events and less likely to discontinue because of death (Table 2). The specific adverse events responsible for cessation (gastrointestinal, palmoplantar dysesthesia

syndrome, fatigue, and other) were identical for SOR + transarterial chemoembolization and SOR (data not presented).

Given more favorable clinical characteristics, it is not unexpected that in unadjusted analyses, survival was markedly better in SOR + transarterial chemoembolization than in SOR patients, with median survival of 418 (IQR 373–497) versus 210 (201–220) days ($P < .0001$) and HR 0.64 (95% CI 0.55–0.73) for death (Fig 1b). Adjusting for baseline CTP score, MELD score, BCLC stage, presence of metastases, and previous receipt of transarterial chemoembolization, SOR + transarterial chemoembolization continued to show reduced risk of death compared with SOR alone (HR 0.73, 95% CI 0.62–0.86; $P = .0001$). Specifically among transarterial chemoembolization-naïve patients, median survival was 417 (IQR 333–658) days for the 107 patients with SOR + transarterial chemoembolization compared with 198 (189–206) days ($P < .0001$) for the 3,569 patients treated with SOR alone. Among previously transarterial chemoembolization-exposed individuals, median survival was 440 (IQR 363–503) days for the 125 patients treated with SOR + transarterial chemoembolization compared with 258 (242–283) days for the 1,093 patients treated with SOR alone ($P = .0004$).

Propensity-Matched Cohort

After propensity matching, 196 early transarterial chemoembolization-exposed patients were matched with 354 non-transarterial chemoembolization patients (Tables 2, 3) exactly matched by CTP, BCLC, MELD, and number of transarterial chemoembolization procedures given before SOR. The matched cohorts were highly balanced for hepatic function and tumor covariates except as follows: (i) There were slightly more women selected for transarterial chemoembolization; (ii) patients undergoing transarterial chemoembolization had larger median tumor size (5.6 vs 4.1 cm median largest tumor diameter); and (iii) patients selected for transarterial chemoembolization were more likely to be prescribed SOR by a hepatologist rather than an oncologist (12 vs 7%; $P = .01$). By Cox proportional hazards and Kaplan-Meier methods stratified by previous receipt of transarterial chemoembolization, CTP score, MELD score, and BCLC stage, SOR + transarterial chemoembolization was associated with a significant survival advantage over SOR alone, with HR 0.63 (95% CI 0.50–0.80; $P = .0001$; Fig 2a). Median survival for SOR + transarterial chemoembolization was 412 (IQR 368–518) days compared with 299 (262–344) days for SOR alone ($P = .0048$). Specifically among patients not exposed to transarterial chemoembolization before SOR, median survival with SOR transarterial chemoembolization was 412 (IQR 323–635) days compared with 260 (239–335) days with SOR alone (HR 0.73, 95% CI 0.57–0.96; $P = .02$; Fig 2b).

Subgroup Analysis

Owing to the sample size, we were underpowered to demonstrate statistically significant benefits in many prespecified subgroups (Fig 3). However, most patient subgroups trended to benefit from SOR transarterial chemoembolization compared with SOR alone, except individuals with total bilirubin >2.0 mg/dL (7% of cohort), platelet count $<50,000/\mu\text{L}$ (3% of cohort), MELD score 15, exactly three tumors (8% of cohort), patients with local tumor invasion (3% of cohort), and BCLC A patients (18% of cohort). The magnitude of benefit

associated with SOR transarterial chemoembolization appeared similar in patients both older and younger than 70 years of age, CTP A and B, patients with MELD scores 6–10 and 11–15, total bilirubin 1 mg/dL and 1.1–2.0 mg/dL, all albumin levels, platelet counts >50,000/ μ L, one or two tumors, with or without macrovascular invasion, with or without metastases, BCLC B and C, and any starting dose of SOR. The most significant reduction in hazard ratio for death occurred with individuals with more than three tumor nodules, with or without macrovascular invasion, and without local invasion or distant metastases. Patients with single large tumors (>5 cm) appeared to benefit less than patients with multiple smaller tumors (2–5 cm).

DISCUSSION

Using the Sorafenib for Hepatocellular Carcinoma in Veterans (SHAVE) cohort of 4,896 US HCC patients prescribed SOR, we identified that ~5% of individuals received trans-arterial chemoembolization within 90 days after initiation of SOR (SOR + transarterial chemoembolization), and the frequency of this practice was stable over time. Patients who receive SOR + transarterial chemoembolization are generally selected for characteristics favorable for survival including reduced age, comorbidity, liver disease severity, and tumor burden. However, after balancing relevant covariates in adjusted analyses and with the use of propensity matching, a significant survival benefit associated with a 27% reduction of risk of death persists.

The combination of SOR transarterial chemoembolization has consistently been shown to be safe and well tolerated (10,12,13), although survival benefits of this combination therapy compared with transarterial chemoembolization alone have not been proven prospectively (14,16,36). To date, no prospective comparative study has evaluated the adjuvant role of transarterial chemoembolization in patients in whom a clinical decision to start SOR has already been made (SOR + transarterial chemoembolization vs SOR alone). The present study suggests that although the presence of local invasion and distant metastases appears to mitigate some the benefit of adjuvant transarterial chemoembolization, early transarterial chemoembolization in combination with SOR remains beneficial in well compensated individuals even in the presence of macrovascular invasion. It may be postulated that enhanced preservation of functional hepatic parenchyma by means of transarterial chemoembolization explains the improved survival observed in these patients. Contrary to what might be expected from locoregional therapy, subgroup analysis also suggests that transarterial chemoembolization provides more significant additive benefit for individuals with multiple moderately-sized tumors (2–5 cm) rather than those with a single large (>5 cm) tumor, possibly owing to differential efficacy of transarterial chemoembolization in tumors >5 cm in size (37,38).

The benefit of SOR + transarterial chemoembolization compared with SOR alone appeared to be significant in both transarterial chemoembolization-naïve and transarterial chemoembolization-refractory patients. Among transarterial chemoembolization-refractory patients, SOR has previously been associated with improved survival compared with continuing transarterial chemoembolization alone (4,6), suggesting an important role for systemic therapy in trans-arterial chemoembolization-refractory patients. Yttrium-90

transarterial radioembolization may also be an effective therapy but does not appear to provide superior results in this setting (39). The present data suggest that continued use of transarterial chemoembolization in addition to initiation of SOR may also prolong survival. These results are consistent with a previous single-center retrospective study in 104 advanced HCC patients with or without portal vein thrombosis that found that SOR + transarterial chemoembolization compared with SOR alone was associated with improved OS (HR 0.498, 95% CI 0.278–0.892) (26). The present results, however, contrast with a single-center retrospective study of 89 patients with main portal vein tumor thrombosis (PVTT) (25), in which no survival difference was evident and median survival ranged from 6 to 7 months. Overall, these data suggest that the potential target population for multimodal therapy in transarterial chemoembolization-refractory HCC and advanced HCC might be those patients with liver-dominant disease, well compensated liver function, and either no PVTT or PVTT not occluding the main portal vein.

This study has several strengths, including the large size of our nationally based cohort, which allowed us to power the study for survival and adequately evaluate several secondary outcomes. Second, this multicenter data from 128 VHA centers affords high external validity, because it reflects recent practice patterns and patient characteristics across the United States in both academic and community centers. Finally, experienced research assistants performed 100% chart confirmation of diagnosis, tumor characteristics, and patient outcomes to provide robust staging and characterization of events leading to drug discontinuation.

This study also has several notable limitations. A large segment of the SOR-exposed subjects were BCLC stage A, for which SOR would not be the preferred modality of treatment. The decision to treat a BCLC A patient with the use of SOR could have been based on patient preference to avoid invasive procedures, biases of the treating clinician, or barriers of access to locoregional therapy. As with any observational cohort study, the potential for unmeasured confounding must be acknowledged. This was a study of mostly male USUS veterans who are older, may be more affected by medical comorbidities, and may or may not have worse outcomes than the general US population. Although much of the tumor staging and receipt of therapy data were abstracted from chart review, ICD diagnosis codes were used to determine comorbidity and underlying liver disease, possibly introducing misclassification bias. No information was collected on veterans who did not primarily receive VA care for HCC; they may have had commercial insurance and different access to specialty care, radioembolization, and transplantation. It was not administratively possible to differentiate selective from nonselective transarterial chemoembolization, the type of embolic agent, or the type and dose of chemotherapeutic agent, and therefore it is possible that technical factors related to the transarterial chemoembolization procedures specifically coadministered with SOR could affect the study's findings. The majority of transarterial chemoembolization used in the VA system during the study period was lipiodol-based conventional transarterial chemoembolization.

CONCLUSION

After adjustment for covariates associated with selection for combination therapy and outcome, addition of transarterial chemoembolization to the treatment plan within 90 days of initiating SOR (SOR + transarterial chemoembolization) was associated with a significant survival advantage over SOR alone, with HR 0.75 (95% CI 0.62–0.92; P .0005). This translated into an increased median survival from 299 (IQR 262–344) days to 412 (368–518) days, an improvement of nearly 4 months. The benefit of SOR transarterial chemoembolization was consistently observed in subgroups with compensated liver disease (MELD score <15, total bilirubin <2 mg/dL) in the absence of portal hypertension (platelet count >150,000/ μ L), independently from previous receipt of transarterial chemoembolization as well as starting dose of SOR. The most significant reduction in HR for death occurred with individuals with more than three tumor nodules, with or without macrovascular invasion, without local invasion or distant metastases. These data should inform future prospective trial design for multimodal therapy in unresectable HCC in whom systemic therapy will be used.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

The Sorafenib for Hepatocellular Carcinoma in Veterans (SHAVE) study was supported by unrestricted research funds from Bayer Healthcare Pharmaceuticals and the Veterans Affairs Human Immunodeficiency Virus, Hepatitis, and Related Conditions Programs, Office of Specialty Care Services. The funding sources had no role in the acquisition, analysis, or interpretation of data.

ABBREVIATIONS

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

REFERENCES

1. Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. *Hepatology* 1999; 30:1434–1440. [PubMed: 10573522]
2. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; 359: 378–390. [PubMed: 18650514]
3. Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009; 10:25–34. [PubMed: 19095497]

4. Ogasawara S, Chiba T, Ooka Y, Kanogawa N, Motoyama T, Suzuki E, et al. Efficacy of sorafenib in intermediate-stage hepatocellular carcinoma patients refractory to transarterial chemoembolization. *Oncology* 2014; 87: 330–341. [PubMed: 25227534]
5. Ohki T, Sato K, Yamagami M, Ito D, Yamada T, Kawanishi K, et al. Efficacy of transcatheter arterial chemoembolization followed by sorafenib for intermediate/advanced hepatocellular carcinoma in patients in Japan: a retrospective analysis. *Clin Drug Investig* 2015; 35:751–759.
6. Arizumi T, Ueshima K, Minami T, Kono M, Chishina H, Takita M, et al. Effectiveness of sorafenib in patients with transcatheter arterial chemoembolization (TACE) refractory and intermediate-stage hepatocellular carcinoma. *Liver Cancer* 2015; 4:253–262. [PubMed: 26734579]
7. Wan X, Zhai X, Yan Z, Yang P, Li J, Wu D, et al. Retrospective analysis of transarterial chemoembolization and sorafenib in chinese patients with unresectable and recurrent hepatocellular carcinoma. *Oncotarget* 2016.
8. Wu J, Li A, Yang J, Lu Y, Li J. Efficacy and safety of TACE in combination with sorafenib for the treatment of TACE-refractory advanced hepato-cellular carcinoma in Chinese patients: a retrospective study. *Onco Targets Ther* 2017; 10:2761–2768. [PubMed: 28603426]
9. Varghese J, Kedarisetty C, Venkataraman J, Srinivasan V, Deepashree T, Uthappa M, et al. Combination of TACE and sorafenib improves outcomes in BCLC stages B/C of hepatocellular carcinoma: a single centre experience. *Ann Hepatol* 2017; 16:247–254. [PubMed: 28233748]
10. Zhao Y, Wang WJ, Guan S, Li HL, Xu RC, Wu JB, et al. Sorafenib Combined with transarterial chemoembolization for the treatment of advanced hepatocellular carcinoma: a large-scale multicenter study of 222 patients. *Ann Oncol* 2013; 24:1786–1792. [PubMed: 23508822]
11. Erhardt A, Kolligs F, Dollinger M, Schott E, Wege H, Bitzer M, et al. TACE plus sorafenib for the treatment of hepatocellular carcinoma: results of the multicenter, phase II SOCRATES trial. *Cancer Chemother Pharmacol* 2014; 74:947–954. [PubMed: 25173458]
12. Chao Y, Chung YH, Han G, Yoon JH, Yang J, Wang J, et al. The combination of transcatheter arterial chemoembolization and sorafenib is well tolerated and effective in asian patients with hepatocellular carcinoma: final results of the START trial. *Int J Cancer* 2015; 136:1458–1467. [PubMed: 25099027]
13. Cosgrove DP, Reyes DK, Pawlik TM, Feng AL, Kamel IR, Geschwind JF. Open-label single-arm phase ii trial of sorafenib therapy with drug-eluting bead transarterial chemoembolization in patients with unresectable hepatocellular carcinoma: clinical results. *Radiology* 2015; 277:594–603. [PubMed: 26069923]
14. Kudo M, Imanaka K, Chida N, Nakachi K, Tak WY, Takayama T, et al. Phase III study of sorafenib after transarterial chemoembolisation in Japanese and Korean patients with unresectable hepatocellular carcinoma. *Eur J Cancer* 2011; 47:2117–2127. [PubMed: 21664811]
15. Sansonno D, Lauletta G, Russi S, Contedua V, Sansonno L, Dammacco F. Transarterial chemoembolization plus sorafenib: a sequential therapeutic scheme for HCV-related intermediate-stage hepatocellular carcinoma: a randomized clinical trial. *Oncologist* 2012; 17: 359–366. [PubMed: 22334456]
16. Lencioni R, Llovet JM, Han G, Tak WY, Yang J, Guglielmi A, et al. Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: the SPACE trial. *J Hepatol* 2016; 64:1090–1098. [PubMed: 26809111]
17. Meyer T, Fox R, Ma YT, Ross PJ, James MW, Sturgess R, et al. Sorafenib in combination with transarterial chemoembolisation in patients with unresectable hepatocellular carcinoma (TACE 2): a randomised placebo-controlled, double-blind, phase 3 trial. *Lancet Gastroenterol Hepatol* 2017; 2:565–575. [PubMed: 28648803]
18. Zhang L, Hu P, Chen X, Bie P. Transarterial chemoembolization (TACE) plus sorafenib versus TACE for intermediate or advanced stage hepato-cellular carcinoma: a meta-analysis. *PLoS One* 2014; 9:E100305. [PubMed: 24945380]
19. Liu L, Chen H, Wang M, Zhao Y, Cai G, Qi X, Han G. Combination therapy of sorafenib and TACE for unresectable HCC: a systematic review and meta-analysis. *PLoS One* 2014; 9:E91124. [PubMed: 24651044]

20. Hu MD, Jia LH, Liu HB, Zhang KH, Guo GH. Sorafenib in combination with transarterial chemoembolization for hepatocellular carcinoma: a meta-analysis. *Eur Rev Med Pharmacol Sci* 2016; 20:64–74. [PubMed: 26813455]
21. Wang G, Liu Y, Zhou SF, Qiu P, Xu L, Wen P, et al. Sorafenib combined with transarterial chemoembolization in patients with hepatocellular carcinoma: a meta-analysis and systematic review. *Hepatol Int* 2016; 10: 501–510. [PubMed: 26856326]
22. Zeng J, Lv L, Mei ZC. Efficacy and safety of transarterial chemoembolization plus sorafenib for early or intermediate stage hepato-cellular carcinoma: a systematic review and meta-analysis of randomized controlled trials. *Clin Res Hepatol Gastroenterol* 2016; 40: 688–697. [PubMed: 27339594]
23. Zhang X, Wang K, Wang M, Yang G, Ye X, Wu M, Cheng S. Transarterial chemoembolization (TACE) combined with sorafenib versus TACE for hepatocellular carcinoma with portal vein tumor thrombus: a systematic review and meta-analysis. *Oncotarget* 2017; 8:29416–29427. [PubMed: 28177886]
24. Reiss KA, Yu S, Mamtani R, Mehta R, d'Addeo K, Wileyto EP, et al. Starting dose of sorafenib for the treatment of hepatocellular carcinoma: a retrospective, multi-institutional study. *J Clin Oncol* 2017; 35: 3575–3581. [PubMed: 28872925]
25. Zhang Y, Fan W, Wang Y, Lu L, Fu S, Yang J, et al. Sorafenib with and without transarterial chemoembolization for advanced hepatocellular carcinoma with main portal vein tumor thrombosis: a retrospective analysis. *Oncologist* 2015; 20:1417–1424. [PubMed: 26446238]
26. Wu FX, Chen J, Bai T, Zhu SL, Yang TB, Qi LN, et al. The safety and efficacy of transarterial chemoembolization combined with sorafenib and sorafenib mono-therapy in patients with BCLC stage B/C hepatocellular carcinoma. *BMC Cancer* 2017; 17:645. [PubMed: 28899349]
27. Lo Re V, 3rd, Lim JK, Goetz MB, Tate J, Bathulapalli H, Klein MB, et al. Validity of diagnostic codes and liver-related laboratory abnormalities to identify hepatic decompensation events in the Veterans Aging Cohort Study. *Pharmacoepidemiol Drug Saf* 2011; 20:689–699. [PubMed: 21626605]
28. Bush K, Kivlahan DR, McDonnell MB, Fihn SD, Bradley KA. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test. *Arch Intern Med* 1998; 158:1789–1795. [PubMed: 9738608]
29. Jepsen P, Vilstrup H, Lash TL. Development and validation of a comorbidity scoring system for patients with cirrhosis. *Gastroenterology* 2014; 146:147–156. [PubMed: 24055278]
30. Kim WR, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, et al. Hyponatremia and mortality among patients on the liver-transplant waiting list. *N Engl J Med* 2008; 359:1018–1026. [PubMed: 18768945]
31. Kaplan DE, Dai F, Aytaman A, Baytarian M, Fox R, Hunt K, et al. Development and performance of an algorithm to estimate the Child-Turcotte-Pugh score from a national electronic healthcare database. *Clin Gastroenterol Hepatol* 2015; 13 2333–2341.e1–6. [PubMed: 26188137]
32. Pugh RN, Murray-Lyon IM, Dawson JL, Petroni MC, Williams R. Tran-section of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973; 60:646–649. [PubMed: 4541913]
33. Bruix J, Sherman M. American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. *Hepatology* 2011; 53:1020–1022. [PubMed: 21374666]
34. Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin Liver Dis* 1999; 19:329–338. [PubMed: 10518312]
35. Sohn MW, Arnold N, Maynard C, Hynes DM. Accuracy and completeness of mortality data in the Department of Veterans Affairs. *Popul Health Metr* 2006; 4:2. [PubMed: 16606453]
36. Hoffmann K, Ganten T, Gotthardt D, Radeleff B, Settmacher U, Kollmar O, et al. Impact of neo-adjuvant sorafenib treatment on liver transplantation in HCC patients—a prospective, randomized, double-blind, phase III trial. *BMC Cancer* 2015; 15:392. [PubMed: 25957784]
37. Malagari K, Pomoni M, Moschouris H, Bouma E, Koskinas J, Stefanidou A, Marinis A, et al. Chemoembolization with doxorubicin-eluting beads for unresectable hepatocellular carcinoma: five-year survival analysis. *Cardiovasc Intervent Radiol* 2012; 35: 1119–1128. [PubMed: 22614031]

38. Hayashi K, Ina H, Tezuka M, Okada Y, Irie T. Local therapeutic results of computed tomography-guided transcatheter arterial chemoembolization for hepatocellular carcinoma: results of 265 tumors in 79 patients. *Cardiovasc Intervent Radiol* 2007; 30:1144–1155. [PubMed: 17909884]
39. Vilgrain V, Bouattour M, Sibert A, Lebtahi R, Ronot M, Pageaux G-P, et al. SARAH: a randomised controlled trial comparing efficacy and safety of selective internal radiation therapy (with yttrium-90 microspheres) and sorafenib in patients with locally advanced hepatocellular carcinoma. *J Hepatol* 2017; 66(1 Suppl):S85–S86.

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.

Figure 1.

(a) Percentage of patients receiving transarterial chemoembolization after initiation of sorafenib by year. (b) Kaplan-Meier survival curves for patients receiving transarterial chemoembolization after initiation of sorafenib (S + T) or sorafenib alone (S) without adjustments. *P* value by log-rank test. When evaluating the first 730 days of follow-up in isolation, SOR þ transarterial chemoembolization is associated with a reduced risk of death, with hazard ratio 0.57 (95% confidence interval 0.49–0.65; $P = 9.9 \times 10^{-16}$).

Figure 2.

Kaplan-Meier survival curves for propensity-matched patients receiving or not receiving transarterial chemoembolization (T) after sorafenib (S) in propensity matched cohort: **(a)** Propensity-matched cohort of 550 subjects (196 S + T and 354 S alone) matched by Child-Turcotte-Pugh score, Barcelona Clinic Liver Cancer stage, Model for End-Stage Liver Disease score, and previous receipt of T. **(b)** Kaplan-Meier survival curves in transarterial chemoembolization-exposed (T+) patients receiving S + T or S alone.

Figure 3.

Effect of sorafenib + transarterial chemoembolization compared with sorafenib alone in clinically important subgroups. Forest plot demonstrating number of patients, hazard ratio with 95% confidence interval, and median survival for each subgroup analyzed. Hazard ratio <1 favors sorafenib + transarterial chemoembolization compared with sorafenib alone.

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.

* $P < .05$.

Table 2.

Characteristics of Unmatched and Propensity-Matched Cohorts

Characteristic	Unmatched Cohort			Propensity Matched Cohort		
	Transarterial chemoembolization within 90 d after sorafenib	Sorafenib alone	<i>P</i> value	Transarterial chemoembolization within 90 d after sorafenib	Sorafenib alone	<i>P</i> value
n	232	4,662		196	354	
No. of transarterial chemoembolization	1 (1–2)	0 (0–0)	<.0001 *	2 (1–2)	0 (0–0)	<.0001
No. of transarterial chemoembolization	1 (0–2)	0 (0–0)	<.0001 *	0(0–1)	0 (0–1)	.19
before sorafenib No. of transarterial chemoembolization before Sorafenib, 0/1/2/3/>3	107/66/29/22/8	3569/514/292/130/157	<.0001 *	105/55/17/15/4	209/90/29/20/6	.84
Age, y	62 (59–66)	62 (59–67)	.28	62 (58–66)	62 (59–66)	.43
Male sex, %	97%	99%	.021	97%	100%	.006 *
Race/ethnicity			.01			.73
Asian	2 (0.9%)	22 (0.5%)		1 (0.5%)	2 (0.6%)	
Black	65 (28.3%)	1205 (25.7%)		57 (29.1%)	94 (26.6%)	
Black Hispanic	2 (1.1%)	19 (0.4%)		1 (0.5%)	2 (0.6%)	
Hispanic	35 (14.3%)	359 (7.4%)		30 (15.3%)	36 (10.2%)	
White	106 (46.3%)	2503 (53.9%)		88 (44.9%)	179 (50.6%)	
Other/unknown	22 (9.1%)	563 (12.2%)		19 (9.7%)	41 (11.6%)	
BCLC stage			<.0001 *			1.0
0	2 (1.0%)	0 (0.0%)		1 (0.5%)	2 (0.6%)	
A	23 (11.6%)	227 (5.3%)		35 (17.9%)	64 (18.1%)	
B	108 (54.3%)	1514 (35.4%)		102 (52.0%)	184 (52.0%)	
C	66 (33.2%)	2322 (54.3%)		57 (29.1%)	102 (28.8%)	
D	0 (0.0%)	216 (5.0%)		1 (0.5%)	2 (0.6%)	
Cirrhosis comorbidity score			.06			.57
0	54 (23.3%)	1255 (26.9%)		47 (24.0%)	103 (29.1%)	
1 +0	82 (35.3%)	1372 (29.4%)		72 (36.7%)	102 (28.8%)	
1 +1	26 (11.2%)	367 (7.9%)		21 (10.7%)	35 (9.9%)	
3+0	11 (4.7%)	277 (5.9%)		9 (4.6%)	20 (5.6%)	
3+1	38 (16.4%)	731 (15.6%)		28 (14.3%)	59 (16.7%)	
5+0	9 (3.9%)	313 (6.7%)		9 (4.6%)	19 (5.4%)	
5+1	12 (5.2%)	356 (7.6%)		10 (5.1%)	16 (4.5%)	
CTP score	6(5–7)	6(5–7)	<.0001 *	6 (5–6)	6(5–6)	1.0
MELD score	13 (11–15)	14 (12–19)	<.0001 *	13 (11–15)	13 (11–15)	.93
AFP	74 (12–855)	124 (13–1589)	<.0001 *	89 (12–855)	62 (11–1106)	.75
ECOG PS >2	1.3%	4.3%	.01	0.5%	0.6%	1.0
No. of tumors	3 (1 –5)	4(1–5)	.007 *	3 (2–5)	4(2–5)	.17

Characteristic	Unmatched Cohort			Propensity Matched Cohort		
	Transarterial chemoembolization within 90 d after sorafenib	Sorafenib alone	<i>P</i> value	Transarterial chemoembolization within 90 d after sorafenib	Sorafenib alone	<i>P</i> value
Largest tumor size	5.5 (3.0–7.4)	5.5 (3.4–8.8)	.11	5.6 (3.1–7.9)	4.1 (2.5–6.7)	.015 *
Macrovascular invasion	17%	29%	<.0001 *	18%	18%	.86
Extrahepatic metastases	6%	18%	<.0001 *	6%	5%	.71
Local invasion	3%	6%	.06	3%	1%	.19
Prescribed by GI/hepatologist	35 (15.2%)	305 (6.6%)	<.0001 *	12%	7%	.01 *
Sorafenib utilization						
Total pills received	360 (180–728)	240 (120–496)	<.0001 *	360 (185–758)	360 (120–660)	.23
Total fills	4(2–9)	3 (1–6)	<.0001 *	4(2–9)	4 (2–7)	.06
Total medication days	120 (60–253)	240 (120–496)	<.0001 *	179 (69–387)	126(44–276)	.005 *
Starting dose, mg/d	800 (400–800)	800 (400–800)	.31	800 (400–800)	800 (400–800)	.72
Average dose, mg/d	737 (523–800)	782 (457–800)	.54	720 (523–800)	775 (516–800)	.19
Sorafenib cessation			.0035 *			.21
Adverse effects	29%	21%		26%	20%	
Progression	29%	29%		27%	36%	
Functional decline	14%	18%		13%	11%	
Nonadherence	3%	2%		2%	3%	
Death	10%	18%		9%	14%	
Other/unknown	15%	12%		23%	16%	
Overall survival						
1y	55%	31%	<.0001 *	55%	41%	.001 *
2y	21%	12%	<.0001 *	21%	16%	.13
3y	11%	6%	<.0001 *	11%	9%	.63

Note—Results are presented as n, median (interquartile range), or n (%), or %.

AFP = alpha-fetoprotein; BCLC = Barcelona Clinic Liver Cancer; CTP = Child-Turcotte-Pugh; MELD = Model for End-Stage Liver Disease; ECOG PS = Eastern Cooperative Oncology Group performance status.

* $P < .05$.

Table 3.

Post-Matching Balancing of Covariates Included in the Model

Propensity model covariate	Mean SOR + transarterial chemoembolization	Mean SOR alone	SD control	Mean diff	eQQ med	eQQ mean	eQQ max
Distance	0.08	0.07	0.04	0.01	0.00	0.01	0.10
Age *	62.89	63.18	6.91	-0.30	1.00	0.64	7.00
CTP score *	5.97	5.97	0.96	0.00	0.00	0.01	1.00
BCLC stage *	2.11	2.11	0.71	0.00	0.00	0.02	1.00
Cirrhosis comorbidity score	1.83	1.88	1.84	-0.06	0.00	0.14	1.00
ECOG PS	0.01	0.01	0.07	0.00	0.00	0.00	0.00
MELD score	13.66	13.66	3.48	0.00	0.00	0.04	2.00
Specialty prescribing	0.20	0.09	0.28	0.11	0.00	0.11	8.00
Race/ethnicity	1.98	2.08	2.29	-0.10	0.00	0.15	5.00
Year	2011	2011	2.16	0.10	0.00	0.21	1.00
Male *	0.97	1.00	0.05	-0.03	0.00	0.03	1.00
Sorafenib started at full dose	0.64	0.63	0.48	0.01	0.00	0.01	1.00
Macrovascular invasion	0.18	0.17	0.38	0.01	0.00	0.01	1.00
Metastases present *	0.06	0.06	0.24	0.00	0.00	0.01	1.00
Local Invasion	0.03	0.01	0.11	0.02	0.00	0.02	1.00
Transarterial chemoembolization before Sorafenib *	0.77	0.77	1.05	0.00	0.00	0.12	1.00

BCLC = Barcelona Clinic Liver Cancer; CTP = Child-Turcotte-Pugh; MELD = Model for End-Stage Liver Disease; ECOG PS = Eastern Cooperative Oncology Group performance status.

* Covariate with $P < .01$ in propensity model.