Original Article

Single institution experience of sorafenib for advanced HCC in a US tertiary care hospital

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Background: Sorafenib is first line chemotherapy for advanced hepatocellular carcinoma (HCC). There are little real-world experiences with sorafenib done on US population except for the US arm of the GIDEON study, a phase IV multi-national study. In this context, we present a single institution experience with sorafenib for HCC in a tertiary inner-city safety-net hospital of Chicago.

Methods: We retrospectively analyzed electronic medical records of patients with HCC (confirmed with radiographic criteria and/or biopsy) who received sorafenib from 2009 to 2016. We collected data regarding the demographics, characteristics of tumor, liver cirrhosis, duration of treatment with sorafenib, reported adverse effects with sorafenib and laboratory investigations done at the time of sorafenib initiation. Overall survival was calculated from the time of sorafenib initiation and cases were censored at the date of last follow up, if date of death was not known. Kaplan-Meier curves were estimated to evaluate the prognostic significance of various clinical variables.

Results: Fifty-nine patients received sorafenib in the study period and the median overall survival was 7 months (25–75 percentile =3–15 months). Alcohol was the leading cause of cirrhosis, 64% of them had Child-Turcotte-Pugh (CTP) class A cirrhosis or did not have cirrhosis and 73% had Barcelona stage C HCC at the time of sorafenib initiation. Close to half of them suffered from adverse effects of sorafenib, most common being those involving skin and gut. Patients with CTP class A cirrhosis or no cirrhosis (median OS 39 *vs.* 16 months, log rank test 3.913, P=0.048), absence of extrahepatic spread (EHS) (median OS 39 *vs.* 9 months, log rank test 5.632, P=0.018) and hepatitis C virus (HCV) infection (median OS 39 *vs.* 9 months, log rank test 5.015, P=0.025) had better survival.

Conclusions: Overall survival of patients with HCC treated with sorafenib in US is lower than those observed in cohorts from Europe or Japan. HCV infection could be a marker of benefit in those treated with sorafenib for HCC. Further studies to confirm this association and understand it's pathophysiologic basis could be useful in development of other therapeutic options for advanced HCC.

Keywords: Hepatocellular carcinoma (HCC); sorafenib; survival analysis

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Introduction

Sorafenib is an orally administered small molecule tyrosine kinase inhibitor that has anti-angiogenic and pro-apoptotic effects (1,2). It's the first-line systemic therapy for advanced hepatocellular carcinoma (HCC) approved by U.S. Food and Drug Administration (3). Two phase III randomized controlled trials showed benefit of overall survival with sorafenib in patients with advanced HCC and Child-Turcotte-Pugh (CTP) class A liver function

(4,5). A phase II trial proved its safety in CTP class B cirrhosis (6). Many observational studies, including the Global investigation of therapeutic decisions in HCC and of its treatment with sorafenib (GIDEON) study have also demonstrated the efficacy of sorafenib in advanced HCC (7). However, a recent study on Medicare data has questioned the applicability of the former phase III trials to a US population (8).

There has also been interest in identifying prognostic and predictive factors for survival in patients with advanced HCC treated with sorafenib. A *post hoc* sub group analysis of the phase III trials identified absence of extrahepatic spread (EHS), hepatitis C virus (HCV) infection and low neutrophil-to-lymphocyte (NLR) ratio as predictors of greater overall survival benefit (9). Observational studies done in Europe and South-East Asia have found a variety of variables to be of predictive and prognostic value (10-13). In the present study done at an inner-city safety net hospital of Chicago, we aimed to evaluate the adverse effect profile, outcomes and identify predictive and prognostic factors for survival associated with use of sorafenib in HCC.

Methods

We retrospectively reviewed the electronic medical records of adult patients (age >18 years) with HCC who presented to John H. Stroger Hospital of Cook County, Chicago, IL, from January 01, 2009 through July 31, 2015. We identified potential patients using ICD-9 code (= 155) and/or ICD-10 code (= C22) for malignant neoplasm of liver and intrahepatic biliary duct. We confirmed the histopathological or imaging diagnosis (intense enhancement during arterial phase followed by "washout patter" during delayed phase, seen on triple phase CT or magnetic resonance imaging in patients with cirrhosis) and included patients who received sorafenib in our analysis. Patients enrolled in clinical trials, who received oncologic care in another hospital or those who received additional systemic chemotherapeutic agents were excluded. The present study was approved by the Institutional Review Board of Cook County Health & Hospitals System, Chicago. The database was set up and maintained by the Department of Medicine, Cook County Health & Hospitals System.

Sorafenib dosing

Sorafenib was started at daily dose of 800 mg in all patients. As per the discretion of the treating medical oncologist, it was discontinued with the development of an adverse event or progression of disease. In some patients, the dose was decreased if the daily 800 mg dose was not tolerated.

Data collection

Eligible patients were censored if there was discontinuation of follow up. We collected data pertaining to patient demographics, tumor, management plans and laboratory investigations, recorded at the time of sorafenib initiation. These include age, gender, race, date of death, etiology of liver disease, CTP class, presence of EHS, portal vein invasion, Barcelona stage of HCC, previous locoregional therapy, duration of sorafenib therapy, adverse events recorded by the treating physician and laboratory values [neutrophil, lymphocyte, hemoglobin, platelet, international normalized ratio (INR), albumin, aspartate aminotransferase, total bilirubin]. EHS was defined as the presence of metastases to abdominal lymph nodes or other solid organs. Portal vein invasion was defined as evidence of it seen on any form of imaging.

Data analysis

Descriptive data was summarized using mean and percentages for continuous and categorical variables, respectively. Overall survival was presented as median with interquartile range. It was calculated as the time from sorafenib initiation to death. Patients with treatment duration greater than 1 month were included in the Kaplan-Meier survival comparisons, to identify potential predictive and prognostic factors. Log rank test was used to compare survival curves. All assumptions of Kaplan-Meier curves were met. Chi square test and Fischer's exact test were used to compare frequency of categorical variables and find associations. Student's *t* test was used to compare means of two groups. All assumptions for Chi-square and Student's *t* test were met. P value of lesser than or equal to 0.05 was considered to statistically significant. SPSS 21 (IBM Corp. Released 2012. Version 21.0. Armonk, NY, USA) was used for the data analysis.

Results

Fifty-nine patients received sorafenib in the study period. Nineteen of them died during the follow up period. Mean age of the population was 57.6 years (standard deviation 8.4 years) and 81% of them were male. Predominant etiologies

Table 1 Baseline characteristics of the cohort

Variable (n=59)	Mean ± SD or number (%)
Age (years)	57.6±8.4
Males	48 (81%)
Etiology	
Hepatitis B	15 (25%)
Hepatitis C	27 (46%)
Alcohol	37 (63%)
Barcelona staging	
A	7 (12%)
B	9 (15%)
C	43 (73%)
CTP class	
A or no cirrhosis	38 (64%)
B	21 (36%)
Extrahepatic spread	20 (34%)
Portal vein invasion	24 (41%)
Previous locoregional therapy	14 (24%)
Died during follow up	19 (32%)
Hb (in g/dL)	12.8±2
WBC (1,000 s/mL)	7.2±2.5
PLT (1,000 s/mL)	211±132
S. Cr (mg/dL)	0.8±0.2
Sodium (mEq/mL)	135±13.1
INR	1.2±0.2
Alb (mg/dL)	3.3±0.6
AFP	19,664±58,743
T Bili (mg/dL)	1.5±1.44

Continuous and categorical variables are presented as mean ± standard deviation and number (percentage), respectively. SD, standard deviation; CTA, Child's Turcot Pugh; Hb, Hemoglobin; WBC, white cell count; PLT, platelets; S Cr., Serum creatinine; INR, international normalized ratio; AFP, alpha fetoprotein; T Bili, total bilirubin.

of liver disease in the cohort were alcohol (63%), HCV infection (46%) and hepatitis B virus (HBV) infection (25%). Sixty-four percent of them had CTP class A cirrhosis or had no cirrhosis. Most common Barcelona stage of the tumor was stage C (73%) and EHS and portal vein invasion were seen in 34% and 41% of the patients, respectively. Descriptive data pertaining to the baseline characteristics of the patients included in the cohort are summarized in *Table 1*.

Table 2 Adverse effect profile in the cohort

Type of adverse effects noted	Frequency (percentage)
GI side effects	13 (22%)
Skin and HFS	15 (25%)
Hepatic	4 (7%)
Other	5 (8%)

GI, gastrointestinal; HFS, hand foot syndrome.

Safety

Twenty-seven of the patients developed adverse effects with sorafenib. It was discontinued in nineteen of them. Median duration of sorafenib treatment in entire cohort was 4.6 months. Most common adverse effects were hand foot syndrome [15] and diarrhea [13]. These are summarized in *Table 2*.

Outcomes

Median overall survival was 7 months (25–75 percentile = 3–15 months). Patients who had received sorafenib for more than 1 month (n=48) were included into the Kaplan-Meier analysis. Patients with CTP class A cirrhosis or no cirrhosis (median OS 39 *vs.* 16 months, log rank test 3.913, P=0.048), HCV infection (median OS 39 *vs.* 9 months, log rank test 5.015, P=0.025) and absence of EHS (median 39 *vs.* 9 months, log rank test 5.632, P=0.018) had better overall survival. Their respective Kaplan-Meier curves are shown in *Figure 1A,B,C*. Comparison of baseline characteristics of patients with and without HCV infection is shown in *Table 3*. Presence of portal vein invasion (P=0.602), previous locoregional therapy (P=0.084), alcoholic liver disease (P=0.296), HBV infection (P=0.378) and history of adverse effects with sorafenib (P=0.69) did not affect overall survival.

Discussion

To the best of our knowledge, this is the first US single institution experience of sorafenib in advanced HCC. The GIDEON study is the only other published study which

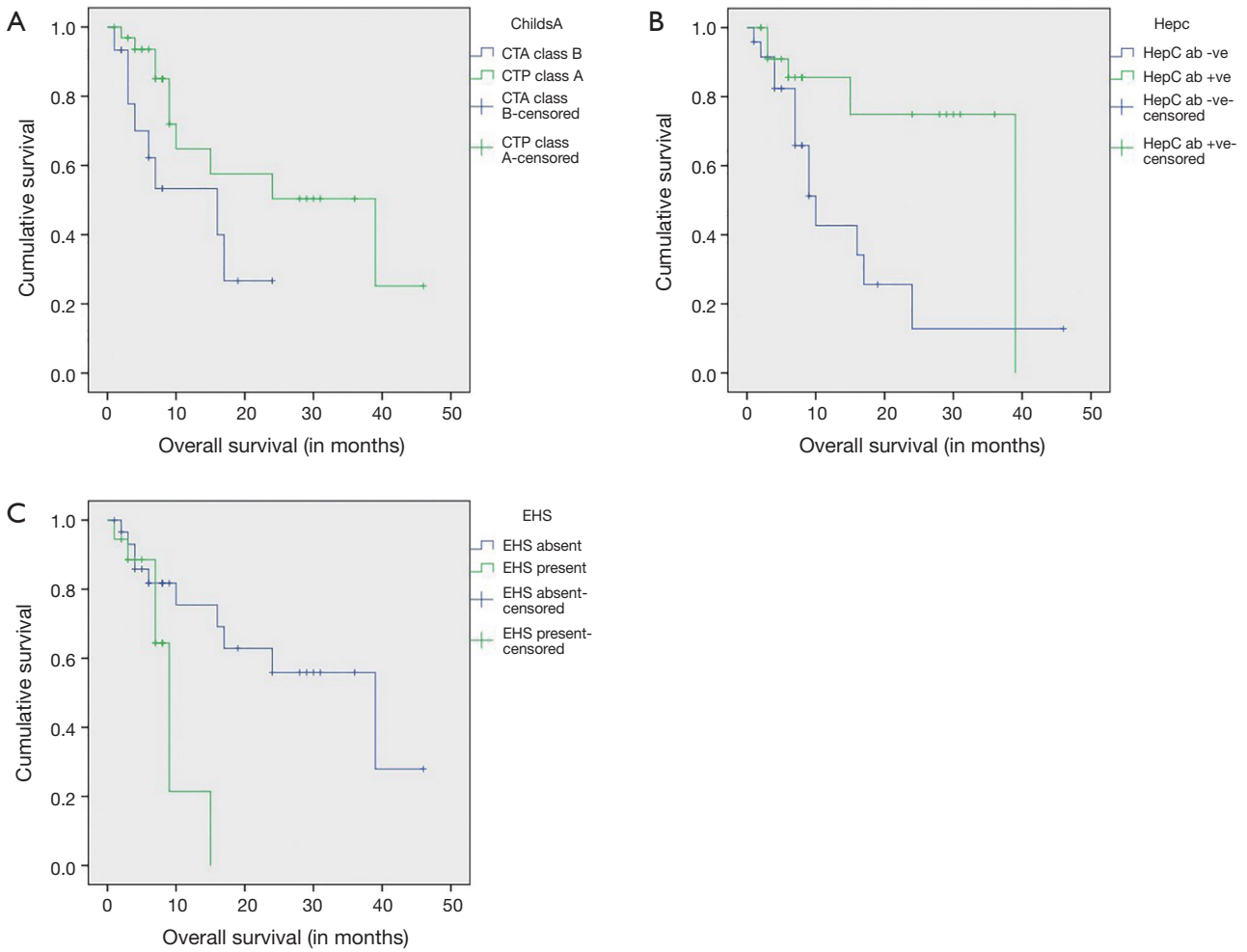

Figure 1 Kaplan-Meier curves of patients stratified by CTP class (A), hepatitis C infection (B) and extrahepatic spread (C). CTA, Child-Turcotte-Pugh; EHS, extrahepatic spread.

describes the real-world experience with sorafenib in a US population (7). Fifty-nine patients were treated with sorafenib for HCC over a span of 6 years in our institution. As the study site was a safety-net hospital serving an underserved population and immigrants, there was a greater proportion of patients with HBV infection (25% *vs.* 14%) and alcohol related liver disease (63% *vs.* 39%) compared to the US arm of GIDEON study. The median duration of treatment was comparable to that of the US arm of GIDEON study (4 *vs.* 4.6 months).

The median survival of our population was slightly lower than of the US arm of GIDEON study (7 *vs.* 8.5 months) (7). A study based on Surveillance, Epidemiology and End Results Program and Medicaid claim data showed a median survival of 3 months from the first prescription of sorafenib in Medicaid patients with advanced HCC in US patients (8). However, it used indirect data sources which could be prone for various forms of bias, making it less reliable. Real world experiences in Europe (14-18) and Japan (19) estimated the median overall survival of patients with advanced HCC after sorafenib initiation to be 10–15 months. Even in the GIDEON study (7), the median overall survival of US patients was lower than Europe and Japan. Interestingly, a prospective multi-center study in Japan has estimated median overall survival of 10.1 months despite higher proportion of patients with EHS and Barcelona stage C (19) than the presented cohort. Even though a head to head comparison of the overall survival from different cohort can't be made due to differences in baseline characteristics of patients, it raises the possibility of social or unknown

Table 3 Baseline characteristics of patients with and without hepatitis C included in the survival analysis

Characteristic	Hep C negative (n=24)	Hep C positive (n=24)	P value
Age	56.67	60.17	0.101
NLR	4.303	3.0838	0.181
AFP	7291	20522	0.368
MELD	13.96	14.21	0.25
Barcelona stage			0.575*
A	3	1	
B	2	4	
C	19	19	
EHS	11	7	0.233
Portal vein invasion	7	12	0.14
Previous locoregional therapy	7	4	0.303
Child's A cirrhosis	18	15	0.35
Faced adverse events	10	11	0.771

*, Fischer's exact test used instead of Chi-square test. NLR, neutrophil-to-lymphocyte ratio; AFP, alpha-fetoprotein; MELD, Model for End-Stage liver disease; EHS extrahepatic spread.

medical or epidemiologic variables affecting survival of patients receiving sorafenib for HCC in US. The pertinent characteristics of the above-mentioned studies along with the median overall survival are shown in *Table 4*.

The adverse effect profile and frequency were similar to those seen in phase III trials and real-world experiences (4,5,15-17). In our study, patients with CTP class A cirrhosis and those without EHS had better survival with sorafenib. This has been replicated in various studies (9,15,16,18) and can be explained by the fact that liver function and extent of cancer spread are established prognostic indicators in all HCC patients (20). Interestingly, HCV infected patients had better survival than those not infected with HCV. A review of the baseline characteristics of these two groups (as shown in *Table 3*) shows that the two comparison groups were largely similar, decreasing the likelihood of confounding. This association was also noted in a post hoc exploratory sub group analysis of the landmark phase III trials for sorafenib in advanced HCC (9). There is evidence to suggest that sorafenib doesn't affect HCV replication *in vivo* (21) and exact pathophysiologic mechanisms of this association are unknown. Sorafenib inhibits multiple tyrosine kinase pathways and also has additional mechanisms independent of tyrosine kinase inhibition (22). It's preferential effect in patients with HCV infection could be due to specific biochemical or biological actions unique to HCV induced carcinogenesis or HCV related HCC metastases. Understanding these mechanisms could be of future significance as it could lead to the development of effective personalized therapies useful for this subset of patients with HCC.

Our study has few limitations. Firstly, it was a retrospective study and is prone to various biases (23), which include absence of control group and possible confounding through unmeasured variables. Secondly, the small sample size may hamper its external validity. We could not perform Cox Regression analysis and due to the limited effective sample size of nineteen, which is equal to the number of deaths recorded in a survival analysis (24). We also could not run subgroup analysis in hepatitis C patients based on viral load or genotype due to the above reason. Thirdly, we did not have information on cause of deaths of the patients.

Conclusions

The median overall survival benefit in patients receiving sorafenib for advanced HCC is probably lesser in US population than in Europe and Japan, cause of which requires investigation. It's relatively safe and its common adverse effects are diarrhea and hand-foot syndrome. HCV infection could be a predictive factor in patients receiving sorafenib for advanced HCC.

Table 4 Pertinent characteristics of studies that investigated role of sorafenib in advanced HCC

Reference of study	Countries studied	No. of patients	Percentage of patients with CTP class A (%)	Percentage of patients with EHS (%)	Percentage of patients with Barcelona stage C (%)	Median OS of patients taking sorafenib (months)
SHARP trial (5)	Europe, USA and Australia	299	95	53	82	10.7
Asia-Pacific trial (4)	SE Asia	226	97.30	52 (to lung)	95.30	6.5
Pressiani *et al.* (18)	Italy	300	79	21	NA	9.1
Iavarone *et al.* (17)	Italy	296	88	75	NA	NA
Ganten *et al.* (15)	Austria and Germany	782	57	36	50	15.1
Hollebecque *et al.* (16)	France	120	83	7	63	11
Non-diabetic arm of Italian study (14)	Italy	233	53	33	76	9
Nakano *et al.* (19)	Japan	312	85	57	85	10.3
US arm of GIDEON study (12)	USA	563	35.3	30	36.2	8.5
Our study	USA	59	64	34	73	7

OS, overall survival; CTP, Child-Turcotte-Pugh; EHS, extrahepatic spread; SHARP, Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol; GIDEON, global investigation of therapeutic decisions in HCC and of its treatment with sorafenib.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The present study was approved by the Institutional Review Board of Cook County Health & Hospitals System, Chicago (No. 16-024).

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