Ref: Ro J Med Pract. 2018;13(4)
DOI: 10.37897/RJMP.2018.4.7

Nexavar in treatment of hepatocellular carcinoma

Gabriela SMIRA[1], MD, Assoc. Prof. Adina CROITORU[3], MD, PhD, Andra VISAN[3], MD, Ioana LUCA[3], MD, Iulia GRAMATICU[3], MD, Florina BUICA[3], MD, Ioana DINU[3], MD, Assoc. Prof. Vladislav BRASOVEANU[2], MD, PhD, Doina HREHORET[2], MD, Prof. Irinel POPESCU[2], MD, PhD

[1]Center of Gastroenterology and Hepatology, Fundeni Clinical Institute, Bucharest
[2]Center of General Surgery and Liver Transplantation, Fundeni Clinical Institute, Bucharest
[3]Department of Oncology, Fundeni Clinical Institute, Bucharest

Abstract

Hepatocellular carcinoma (HCC) is a significant health problem. Globally is the second most common cause of cancer-associated death and the fifth most frequent neoplasm. The main risk factors for the onset of HCC are well recognized, including the presence of cirrhosis, chronic hepatitis C and hepatitis B infections and heavy alcohol consumption. In an early stage disease, there are potentially curative therapies, such as surgical resection, transplantation and loco-regional procedures. However, at the time of diagnosis, a large number of patients present an advanced stage disease, according to the Barcelona Clinic Liver Cancer (BCLC) classification.

Background. Sorafenib chemotherapy is the first-line therapy for patients with hepatocellular carcinoma (HCC) in an advanced stage. The aim of this study was to evaluate prognostic factors of survival in HCC patients treated with sorafenib, in real-life clinical practice.

Methods. We perform an retrospective, non-randomized study and we analyzed 162 patients with HCC who were treated with sorafenib 800 mg/day in Oncology Department of Fundeni Clinical Institute between 2009 and 2016.

Results. Mortality in our patients group was more than 80%, with survival rate about 22 months and a median survival rate 13 months. The patients with liver cirrhosis has a severe evolution compared with those who has hepatitis. We found a good survival rate for HCV infected patients compared with HVB or VHB +VHD etiology. BCLC and Child-Pugh classification have an important role in overall survival.

Keywords: sorafenib, hepatocellular carcinoma, cirrhosis

INTRODUCTION

Hepatocellular carcinoma (HCC) constitutes the fifth most frequent form of cancer worldwide, and it holds the second place in malignancy related mortality (1). Hepatocellular carcinoma (HCC) accounts for 85% to 90% of all primary hepatic malignancies (2,3). In the United States, the incidence of HCC has increased from 1.4 cases per 100,000 in 1976–1980 to approximately 5 cases per 100,000 in 2003-2006 (4-6). The main risk factors for the onset of HCC are well recognized, including the presence of cirrhosis, chronic hepatitis C and hepatitis B infections and heavy alcohol consumption (7).

Corresponding author:
Gabriela Smira, MD
E-mail: smira.gabriela@gmail.com

In an early stage disease, there are potentially curative therapies, such as surgical resection, transplantation and locoregional procedures. However, at the time of diagnosis, a large number of patients present an advanced stage disease, according to the Barcelona Clinic Liver Cancer (BCLC) classification (8).

Molecular-targeted therapeutic strategies offer new hope for effective palliative therapy in livedr cancer. Sorafenib (Nexavar) is an orally available multi-kinase inhibitor acting on several distinct tyrosine kinases. By inhibiting angiogenesis and cellular proliferation, sorafenib can block two of major signalling pathways of HCC expansion (13,14). In a phase 3 SHARP trial involving 602 patients, sorafenib 400 mg was moderately well-tolerated and associated with improved survival in 44% of patients resulting in 3 months extended survival in treated patients (10.7 months in the sorafenib arm versus 7.9 months in the control arm) (15). Sorafenib has established itself as the first option in patients with HCC who can no longer be treated with potentially more effective local therapies.

MATERIALS AND METHODS

We perform an retrospective, non-randomized study and we analyzed 162 patients who were diagnosed with HCC and treated in Oncology Department of Fundeni Clinical Institute between 2009 and 2016.

Sorafenib was given as first line therapy in advanced stage or as second line in intermediate stage patients after locoregional treatment, following assessment and indication from the multidisciplinary group special dedicated to this topic. Therapy regime was 400 mg of sorafenib twice daily, except for those who reduced the dose to 400 mg daily due to adverse events.

OS was measured from the starting date of sorafenib therapy until the date of the last contact.

RESULTS

In our study group, we calculated General Survival (Fig 1).

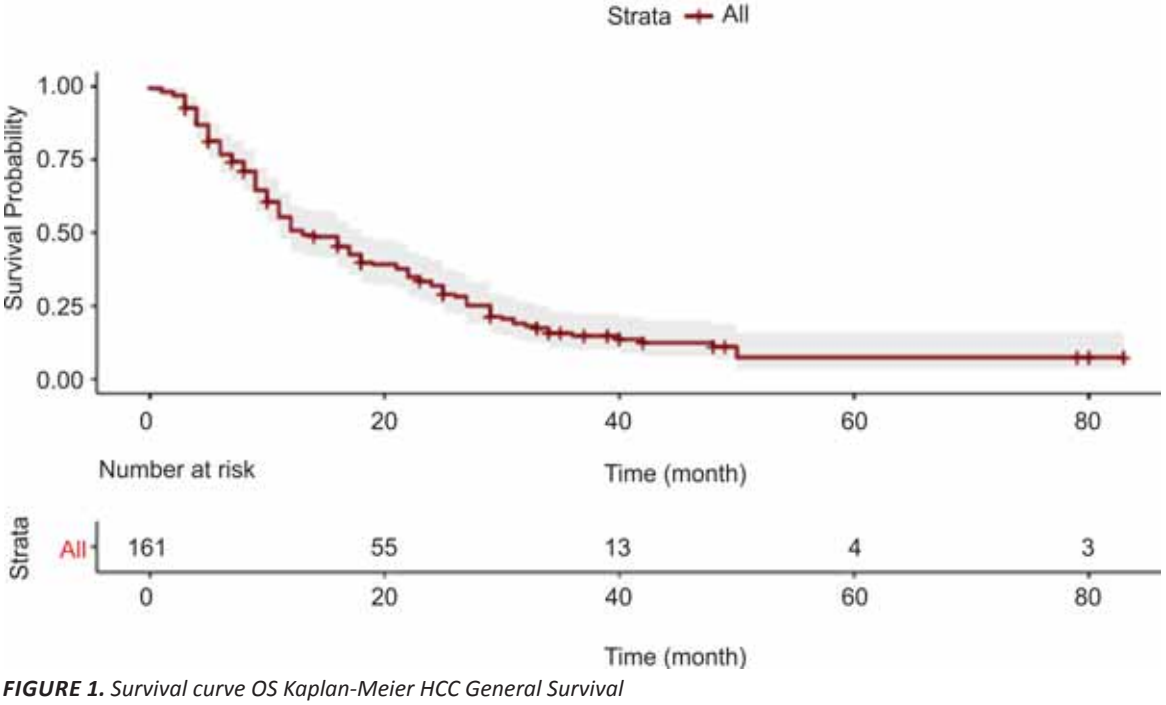

FIGURE 1. *Survival curve OS Kaplan-Meier HCC General Survival*

Strata	Restrictive Media [1]	Mediana	IC95% Mediana
Group	21.60	13.00	11.00 at 18.00

Mortality data:

Strata	Deceased	Survivals	Total
Group	131 (81.36)	30 (18.64)	161

The mortality in our patients group was more than 80%, with survival rate about 22 months and a median survival rate 13 months.

We perform an univariate analysis of OS and risk factors for every analyzed parameter used a long-rank test for compared Kaplan-Meier curves.

Survival based on sex parameter was (Fig. 2):

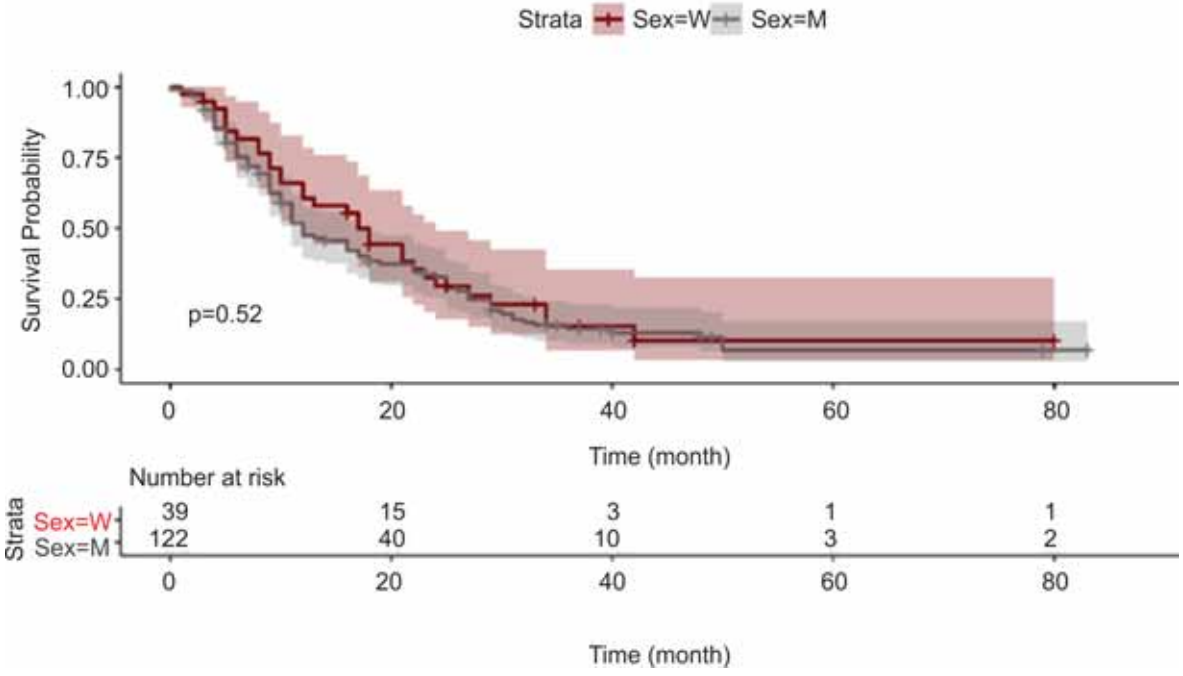

FIGURE 2. *Survival curve OS Kaplan-Meier HCC based on sex parameter*

Strata Sex	Restrictivemedia	Median	IC95% Median
W	23.70	17.00	12.00 at 24.00
M	20.90	12.00	11.00 at 18.00

Even if survival seems to be better for women than men, long-rank test suggested that the differences are not statistically significant.

Strata Sex	Deceased	Survivals	Total
W	31 (79.48)	8 (20.52)	39
M	100 (81.96)	22 (18.04)	122

We can observe a higher mortality for men (82% vs 79.50%). To analyze mortality hazard, we used a Cox regression:

Sex	Coefficient	Wald z	P value	HR [IC95%]
W	REFERENCE	-	-	-
M	0.136	0.662	0.508	1.14 [0.76 at 1.71]

The mortality hazard is 1.14 higher for men compared with women.

We found survival rate based on HCC etiology (Fig. 3):

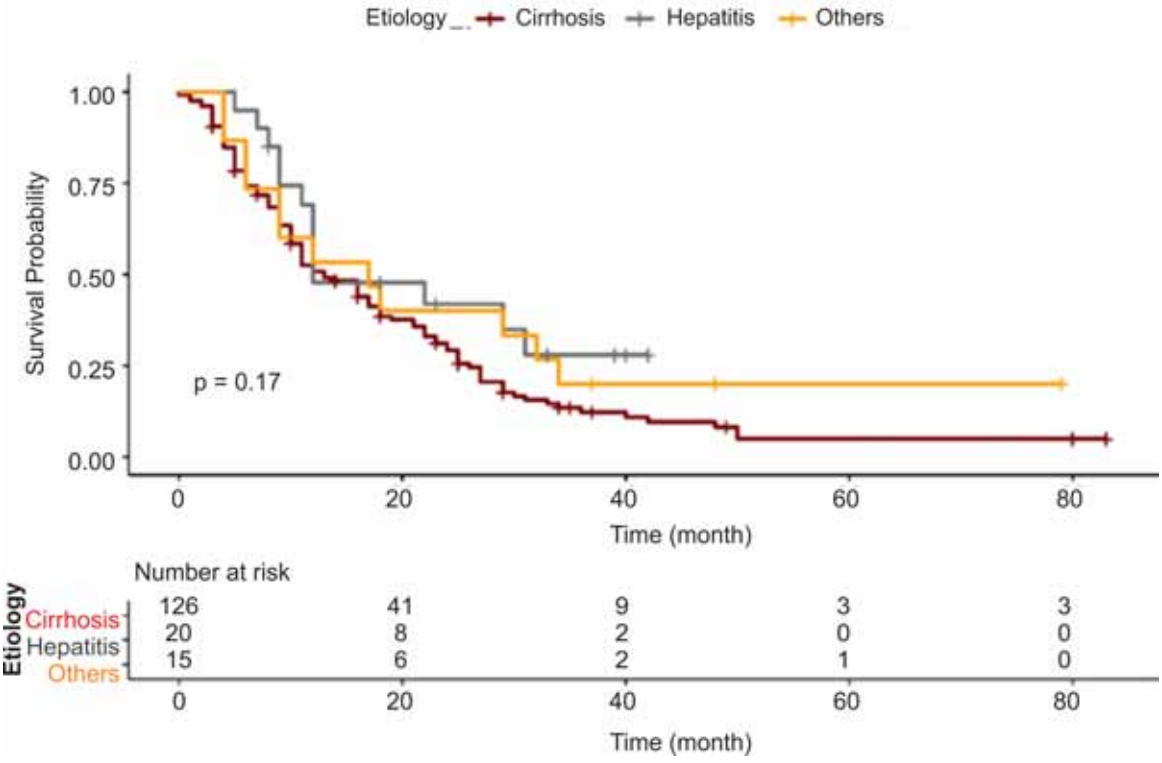

FIGURE 3. *Survival curve OS Kaplan-Meier based on HCC etiology*

Strata Etiology	Restrictive media	Median	IC95% Median
Cirrhosis	19.40	13.00	11.00 at 18.00
Hepatitis	32.60	12.00	12.00 at N/A
Others	27.80	17.00	9.00 at N/A

The survival curves analysis demonstrated severe response for patients with cirrhosis p value for log-rank test is small (p = 0.17).

Strata Etiology	Deceased	Survivals	Total
Cirrhosis	106 (84.12)	20 (15.88)	126
Hepatitis	13 (65.00)	7 (35.00)	20
Others	12 (80.00)	3 (20.00)	15

Cox regression demonstrate a better prognosis for patients with hepatitis compared with those with cirrhosis (a hazard mortality 0.63 lower than cirrhosis) (Fig. 4).

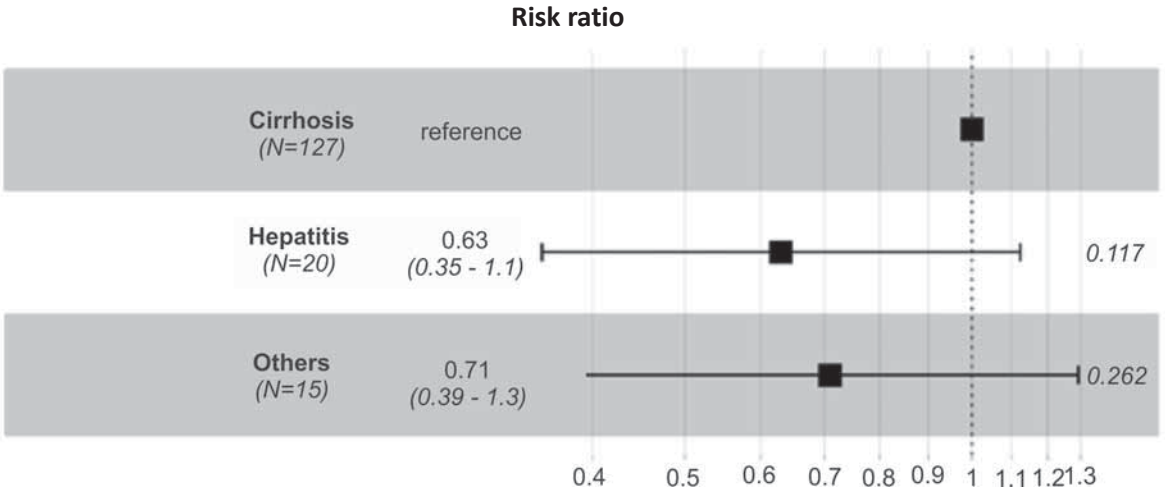

FIGURE 4. *Risk mortality based on etiology*

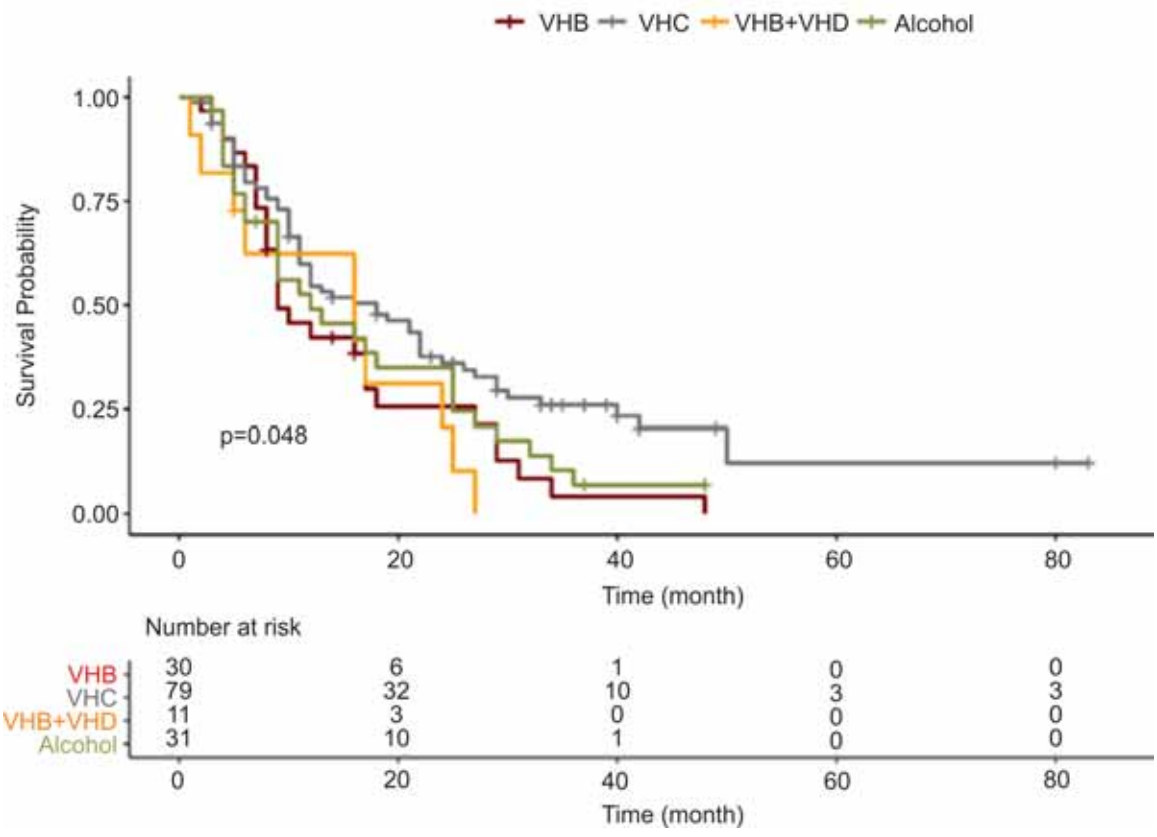

FIGURE 5. *Survival curve OS Kaplan-Meier HCC patients type of infection*

Survival data:

Strata	Restrictive media	Median	IC95% Median
VHB	15.50	9.00	8.00 at 18.00
VHC	22.10	18.00	11.00 at 24.00
VHB+VHD	14.30	16.00	6.00 at N/A
Alcohol	17.20	12.00	9.00 at 25.00

Our analysis shows the best survival rate for HCV infected patients, log-rank test reveals significant statistical differences between at least 2 strata ($p < 0.05$) (Fig 5).

Mortality data:

Strata	Deceased	Survivals	Total
VHB	27 (90.00)	3 (10.00)	30
VHC	58 (73.41)	21 (26.59)	79
VHB+VHD	10 (90.90)	1 (9.10)	11
Alcohol	27 (87.09)	4 (12.91)	31

Cox regression demonstrated that HCV infection has a hazard mortality 2 times lower than HVB infection (HR = 0.58), with statistical significant rate ($p < 0.05$). VHD coinfection doesn't show a more sever prognosis (HR = 1.14 but $p > 0.05$).

Etiology	Coefficient	Wald z	P value	HR [IC95%]
VHB	REFERENCE	-	-	-
VHC	-0.538	-2.282	0.022	0.58 [0.36 at 0.92]
VHB+VHD	0.134	0.362	0.717	1.14 [0.55 at 2.37]
Toxic	-0.149	-0.547	0.584	0.86 [0.50 at 1.47]

Survival analysis based on Child-Pugh classification showed a better survival rate was for Child-Pugh A patients (p = 0.07) compared with Child-Pugh B patients (p = 0.07) (Fig 6).

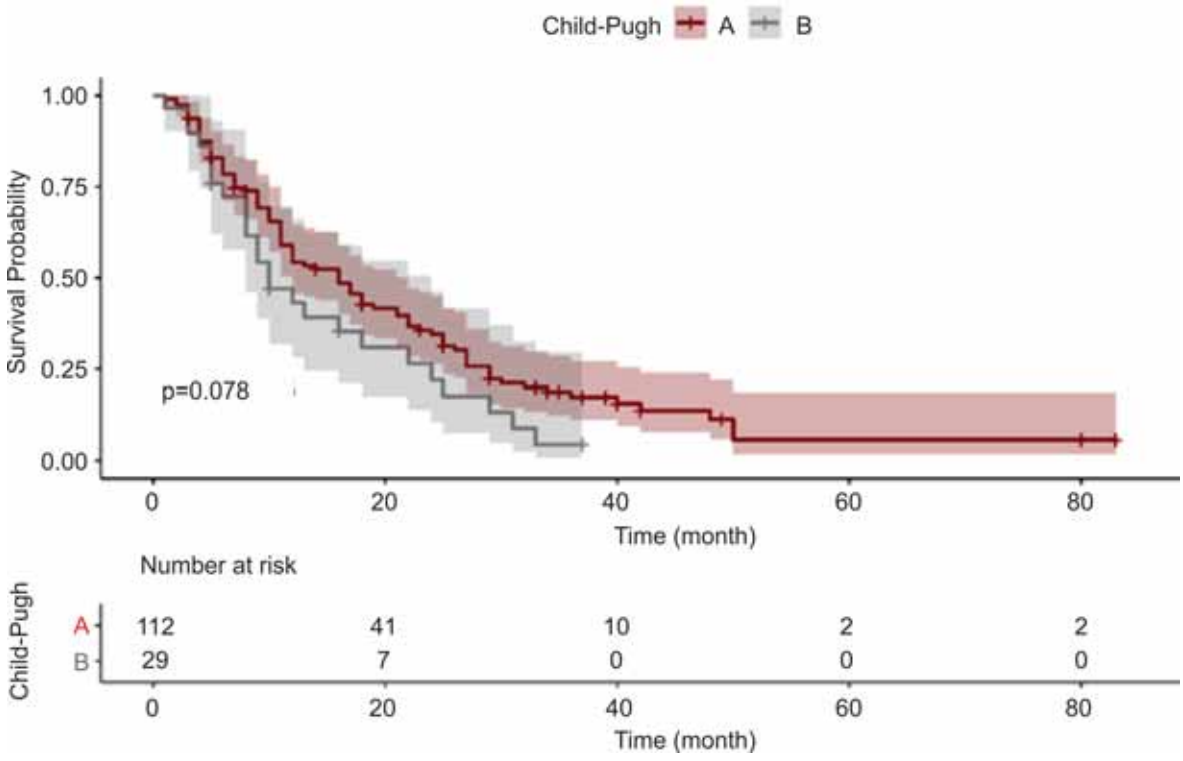

FIGURE 6. *Survival curve OS Kaplan-Meier HCC patients Child-Pugh Classification*

Strata Child-Pugh	Restrictive media	Median	IC95% Median
A	20.70	16.00	12.00 at 22.00
B	15.60	10.00	8.00 at 24.00

Child-Pugh B patients has a decease hazard 1.5 higher compared with Child-Pugh A patients.

Strata Child-Pugh	Deceased	Survivals	Total
A	90 (80.35)	22 (19.65)	112
B	25 (86.20)	4 (13.80)	29

Cox regression:

Child-Pugh	Coefficient	Wald z	P value	HR [IC95%]
A	Reference	-	-	-
B	0.398	1.743	0.081	1.48 [0.95 at 2.33]

Survival analysis based on presence of portal vein thrombosis was (Fig. 7):

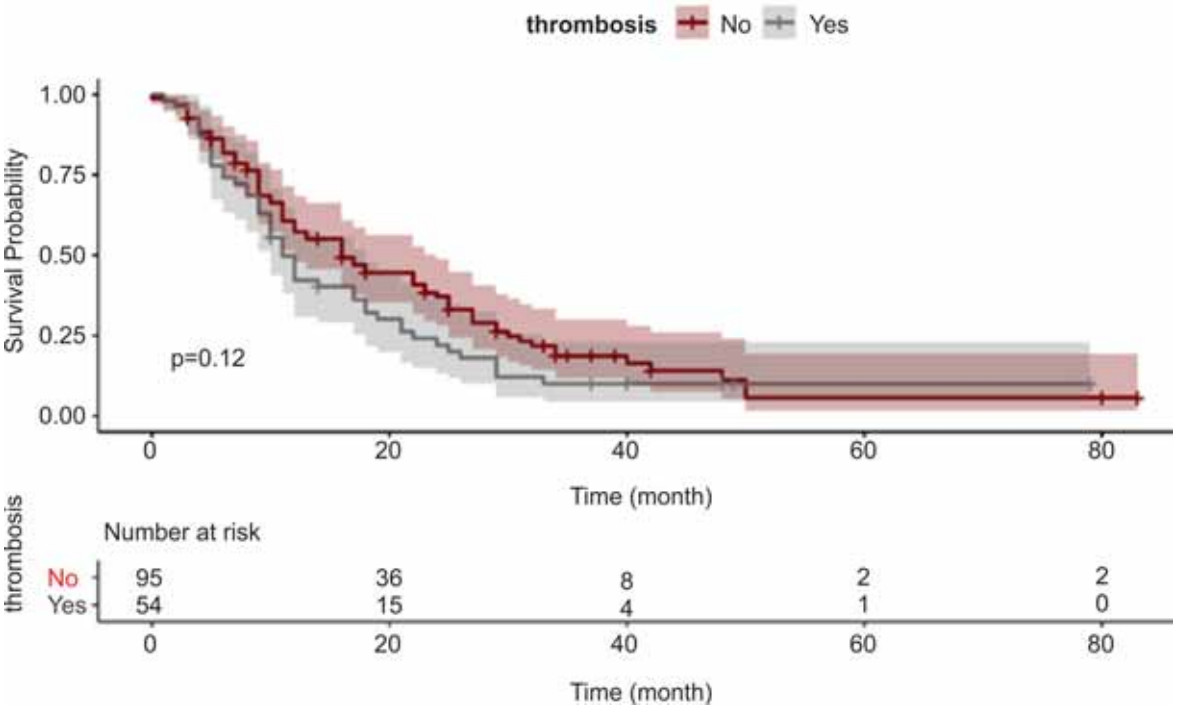

FIGURE 7. *Survival curve OS Kaplan-Meier HCC patients with portal vein thrombosis*

Strata Portal vein thrombosis	Restrictive media	Median	IC95% Median
No	22.80	16.00	12.00 at 24.00
Yes	19.70	11.00	10.00 at 18.00

The patients without portal vein thrombosis have a better survival rate compared with the patients with portal vein thrombosis.

Strata Portal vein thrombosis	Deceased	Survivals	Total
No	74 (77.89)	21 (22.11)	95
Yes	47 (87.03)	7 (12.97)	54

Cox regression demonstrated that the hazard decease is 1.33 higher in portal vein thrombosis group compared with non-portal vein thrombosis patients (p = 0.12) (Fig. 8).

Portal vein thrombosis	Coefficient	Wald z	P value	HR [IC95%]
Absence	REFERENCE	-	-	-
Present	0.287	1.538	0.124	1.33 [0.92 at 1.92]

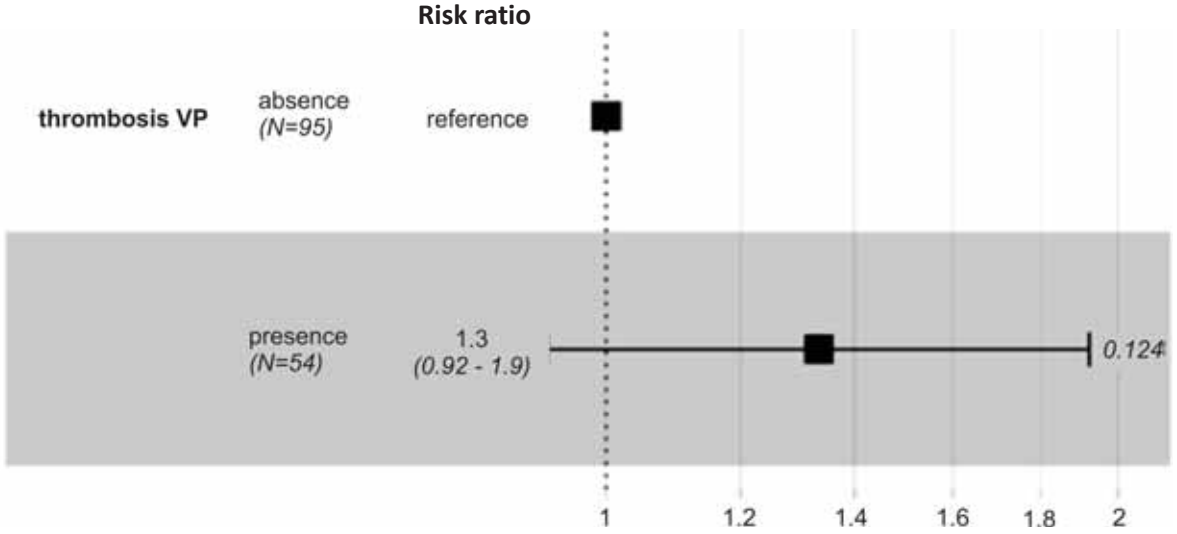

FIGURE 8. *Risk mortality based on portal vein thrombosis*

Survival analysis based on lymph nodes presence showed (Fig. 9):

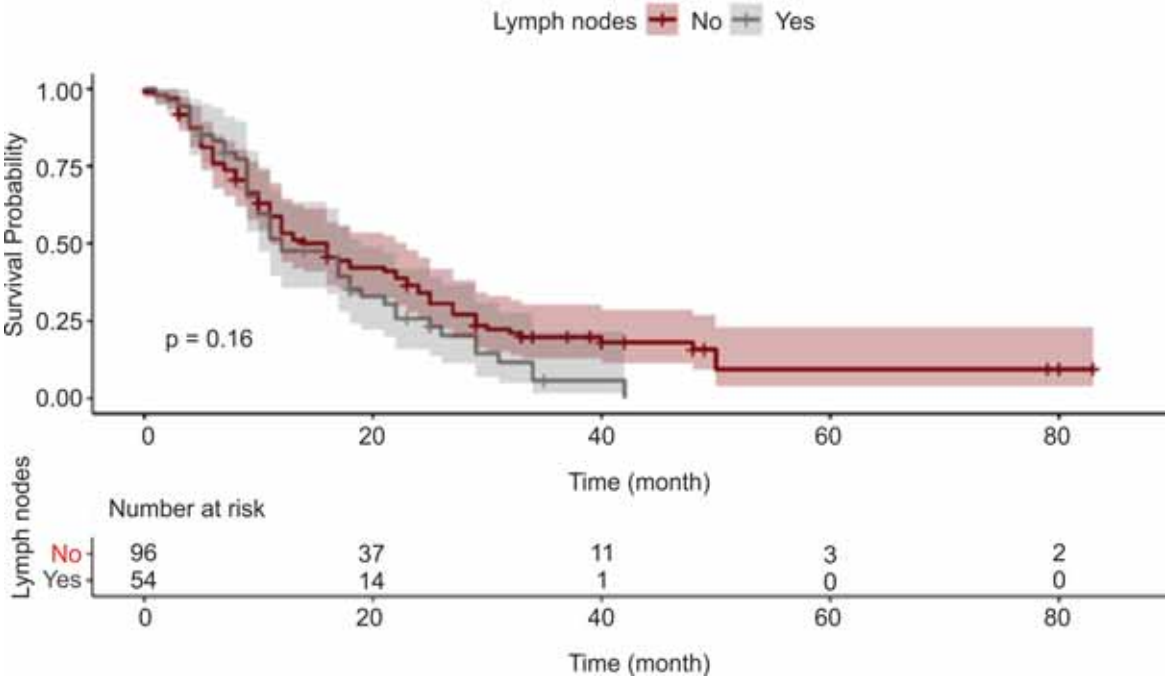

FIGURE 9. *Survival curve OS Kaplan-Meier HCC patients with lymph nodes*

The survival rate is better in the patients group without lymph nodes with a hazard decease 1.3 higher (p = 0.15).

Strata lymph nodes	Restrictive media	Median	IC95% Median
No	21.70	16.00	11.00 at 23.00
Yes	16.60	12.00	10.00 at 19.00

Strata lymph nodes	Deceased	Survivals	Total
No	77 (80.20)	11 (19.80)	96
Yes	45 (83.33)	9 (16.67)	54

Age analysis

Because age is a permanent variable, we used a Cox regression for this analysis.

Cox regresssion:

Variable	Coefficient	Wald z	p Value	HR [IC95%]
Age	0.009	1.195	0.232	1.01 [0.99 at 1.02]

Our analysis does not consider age like a potential hazard factor for mortality (p > 0.05).

Treatment duration analysis is also a Cox regression:

Variable	Coefficient	Wald z	P value	HR [IC95%]
Treatment duration	-0.087	-7.624	< 0.0001	0.91 [0.89 at 0.93]

A longer period of treatment is associated with a low hazard decease, one month more therapy decrease the hazard decease 0.91 times, this effect is consider statistical significant (p < 0.01).

DISCUSSION

Sorafenib is the first FDA-approved systemic therapy for patients with advanced HCC not amenable to treatment by surgical resection or liver transplantation. In clinical practice, sorafenib generally is not given until such patients have failed to respond to locoregional therapies such as transcatheter arterial chemoembolization (TACE). A number of prospective clinical trials have assessed the anti-HCC effects of sorafenib alone, sorafenib with systemic chemotherapy, and sorafenib with locoregional therapy.

In literature, there are 7 sorafenib-alone trials, which included a total of 1,072 patients. Two reports described phase 3 randomized, placebo-controlled clinical trials (16,17), three de-

scribed phase 2 trials (18-20) and two described phase 1 trials (21,22). The percentage of male patients ranged from 71% (18) to 100% (22). Median age ranged from 51 (17) to 72 years (19). Among the five trials providing precise OS data (16-18,20,21), OS ranged from 5 (20) to 15.6 months (21) in the patients who received sorafenib.

The SHARP and Asian-Pacific (16,17) studies were the two highest quality reports (phase 3 randomized, placebo-controlled trials). The large majority of patients in both studies had Child A cirrhosis (95% and 97%), but the frequency of hepatitis B infection was considerably higher in the Asian-Pacific trial (71% vs. 19%). For the sorafenib and placebo groups in the SHARP trial, the OS was 10.7 vs. 7.9 months ($P < 0.05$) (16). For the sorafenib and placebo groups in the Asian-Pacific trial, the OS was 6.5 vs. 4.2 months.

We perfom a study with sorafenib alone to see the efficacy of sorafenib in treating advanced HCC using overall survival. Also we find out the efficacy of sorafenib treatment depending on gender, age, stage of cirrhosis, and etiology of the underlying liver disease (especially hepatitis B and hepatitis C).

Sorafenib provides statistically significant, but clinically modest, improvements in OS (8). The large majority of patients included in the reports were men who had HCC associated with Child-Pugh A cirrhosis (9). Our systematic review does suggest that patients with hepatitis B infection might have a poorer response to sorafenib treatment than patients with hepatitis C. The trial with the highest percentage of hepatitis B patients (90%) described the lowest OS (5 months) and DFS (26%) (10), whereas the trial with the highest percentage of hepatitis C patients (74%) had the longest OS (15.6 months) and the highest DFS (82%) (11). Further studies that directly compare the response to sorafenib in patients who have HCC associated with hepatitis B and C are needed to establish this relationship.

This study confirms the benefit of sorafenib in OS, namely in Child-Pugh A patients. According to the Child-Pugh class, Child-Pugh A patients had a significantly higher median survival versus Child-Pugh B. Therefore, liver function of patients in sorafenib therapy is an important prognostic factor of survival.

CONCLUSIONS

Sorafenib, in daily practice, has proven to be more effective than in registration trials regarding overall survival (SHARP 10.7 months). Also, the median overall survival recorded in this study was slightly longer than in GIDEON study (12.1 months for the 800 mg/day group), probably administrating Sorafenib beyond progression, until patients had clinical benefit.

REFERENCES

1. Parkin DM, Bray F, Ferlay J et al. Global cancer statistics, 2002. *CA Cancer J Clin.* 2005;55:74–108.
2. Pons-Renedo F, Llovet JM. Hepatocellular carcinoma: a clinical update. *MedGenMed.* 2003;5:11.
3. Cancer Facts & Figures 2010. American Cancer Society; Atlanta, Geogia: 2010.
4. El-Serag HB. Epidemiology of hepatocellular carcinoma in USA. *Hepatol Res.* 2007;37 (Suppl 2):S88–94.
5. El-Serag HB, Davila JA, Petersen NJ et al. The continuing increase in the incidence of hepatocellular carcinoma in the United States: An update. *Ann Intern Med.* 2003;139:817–23. [PubMed].
6. El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. *N Engl J Med.* 1999;340:745–50. [PubMed].
7. NHANES III data. 2008.
8. Llovet JM, Ricci S, Mazzaferro V et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med.* 2008;359(4):378-390.
9. Massa ESC et al. Efficacy, safety and impact on quality of life of a treatment with sorafenib in elderly cancer patients with advanced hepatocellular carcinoma. Result of a phase II study. *Annals of Oncology.* 2009;20(Suppl 8):s65.
10. Yau T, Chan P, Ng KK et al. Phase 2 open-label study of single-agent sorafenib in treating advanced hepatocellular carcinoma in a hepatitis B-endemic Asian population: presence of lung metastasis predicts poor response. *Cancer.* 2009;115:428–36.
11. Furuse J, Ishii H, Nakachi K et al. Phase I study of sorafenib in Japanese patients with hepatocellular carcinoma. *Cancer Sci.* 2008;99:159–65.
12. Castroagudin JFME et al. Short-term efficacy and safety of treatment of advanced hepatocellular carcinoma with sorafenib. *Journal of Hepatology.* 2008;48(362 Suppl 2):s141–s142.
13. Wilhelm SM, Carter C, Tang L et al. BAY 43–9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. *Cancer Res.* 2004;64:7099–109.
14. Wilhelm SM, Adnane L, Newell P et al. Preclinical overview of sorafenib, a multikinase inhibitor that targets both Raf and VEGF and PDGF receptor tyrosine kinase signaling. *Mol Cancer Ther.* 2008;7:3129–40.
15. Llovet J et al. Sorafenib improves survival in advanced hepatocellular carcinoma (HCC): Results of a Phase III randomized

placebo-controlled trial (SHARP trial); Proceedings from the American Society of Clinical Oncology Conference; Chicago, IL: 2007.
16. Llovet JM, Ricci S, Mazzaferro V et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359:378–90.
17. Cheng AL, Kang YK, Chen Z 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.
18. Abou-Alfa GK, Schwartz L, Ricci S et al. Phase II study of sorafenib in patients with advanced hepatocellular carcinoma. J Clin Oncol. 2006; 24: 4293–300.
19. Massa ESC et al. Efficacy, safety and impact on quality of life of a treatment with sorafenib in elderly cancer patients with advanced hepatocellular carcinoma. Result of a phase II study. Annals of Oncology. 2009; 20 (Suppl 8):s65.
20. Yau T, Chan P, Ng KK et al. Phase 2 open-label study of single-agent sorafenib in treating advanced hepatocellular carcinoma in a hepatitis B-endemic Asian population: Presence of lung metastasis predicts poor response. Cancer. 2009; 115: 428–36.
21. Furuse J, Ishii H, Nakachi K et al. Phase I study of sorafenib in Japanese patients with hepatocellular carcinoma. Cancer Sci. 2008; 99: 159–65
22. Castroagudin JFME et al. Shor-term efficacy and safety of treatment of advanced hepatocellular carcinoma with sorafenib. Journal of Hepatology. 2008; 48(362 Suppl 2):s141–s142.