Nexavar in treatment of hepatocellular carcinoma

Gabriela SMIRA¹, MD, Assoc. Prof. Adina CROITORU³, MD, PhD, Andra VISAN³, MD, Ioana LUCA³, MD, Iulia GRAMATICU³, MD, Florina BUICA³, MD, Ioana DINU³, MD, Assoc. Prof. Vladislav BRASOVEANU², MD, PhD, Doina HREHORET², MD, Prof. Irinel POPESCU², MD, PhD

¹Center of Gastroenterology and Hepatology, Fundeni Clinical Institute, Bucharest
²Center of General Surgery and Liver Transplantation, Fundeni Clinical Institute, Bucharest
³Department 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).
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 liver 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).

![Survival curve OS Kaplan-Meier HCC General Survival](image)

| Strata | Restrictive Media | Median | IC95% Median |
|--------|------------------|--------|--------------|
| Group  | 21.60            | 13.00  | 11.00 at 18.00 |

| 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):

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

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

The mortality hazard is 1.14 higher for men compared with women.
We found survival rate based on HCC etiology (Fig. 3):

![Survival curve OS Kaplan-Meier based on HCC etiology](image)

**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).

![Number at risk](image)

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).

![Risk ratio](image)

**FIGURE 4.** Risk mortality based on etiology
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):

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

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

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

![Figure 9: Survival curve OS Kaplan-Meier HCC patients with lymph nodes](image)

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

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

**Cox regression:**

| 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).

A longer period of treatment is associated with a low hazard decrease, one month more therapy decrease the hazard decrease 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 loco-regional 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 perform 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.

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