Original article

Sorafenib for Egyptian patients with advanced hepatocellular carcinoma; single center experience

Omar Abdel-Rahman *, Manal Abdelwahab, Mohammed Shaker, Sherif Abdelwahab, Mohammed Elbassiony, Mahmoud Ellithy

Clinical Oncology Department, Faculty of Medicine, Ain Shams University, Abbasya Square, Cairo, Egypt

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KEYWORDS
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Abstract
Background: According to the results of a number of phase 3 randomized studies, sorafenib is the only approved systemic therapy for advanced HCC; however the issue of high economic cost remains challenging; thus we have conducted this retrospective analysis of our HCC patients treated with sorafenib.

Methods: HCC Shams University Hospitals, in the period between 2010 and 2012 were reviewed. Eligible patients were those who had received sorafenib for advanced HCC not eligible for or progressed after surgery or locoregional therapy. We investigated the impact of baseline clinicopathological factors (age, gender, child status, performance score, BCLC tumor stage, cause of chronic liver disease, median baseline alpha fetoprotein level and previous treatment received for HCC) on overall survival (OS) in an adjusted Cox regression model.

Results: 41 patients were included in the analysis fulfilling the inclusion criteria. At a median follow up period of 13 months, the median PFS for the whole group was 4 months; the median OS for the whole group is 6.25 months. Multivariate analysis identified three baseline characteristics that were

Abbreviations: HCC, hepatocellular carcinoma; NCI-CTC, national cancer institute-common toxicity criteria; OS, overall survival; PFS, progression free survival; ITT, intention to treat analysis; CT, computerized tomography; BCLC, Barcelona clinic liver cancer; αFP, Alpha fetoprotein; PS, performance status; CP, child-Pugh; HCV, hepatitis C virus; HBV, Hepatitis B virus; RFA, radiofrequency ablation

* Corresponding author. Tel.: +20 1008541806.
E-mail address: omar.abdelrhman@med.asu.edu.eg (O. Abdel-Rahman).

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Background

Hepatocellular carcinoma (HCC) is the most common liver neoplasm and the fifth most common cancer worldwide [1]. Sorafenib – a multikinase inhibitor – is the first agent which demonstrated survival benefits in patients with unresectable advanced HCC. This significant progress in the treatment of HCC was based upon 2 landmark phase 3 studies (SHARP study in the western population and Asian pacific study in the Asian population) that has been reconfirmed in a number of phase 2 and 3 studies in different parts of the world [2,3]. However when applied to the practice in Egypt, the vast majority of patients enrolled in these landmark studies were in good performance status (PS) 0 or 1 and had a compensated liver function classified as Child Pugh A (CP-A). Conversely, in real practice in Egypt the majority of patients with advanced HCC have compromised liver cirrhosis and significant comorbidity, threatening their general condition and liver function [4]. In spite of the fact that there is no evidence of a survival benefit, many advanced HCC patients in Egypt as well as in other parts of the world with Child–Pugh B liver cirrhosis receive sorafenib monotherapy [5]. Additionally, the pathogenesis of HCC in Egypt is different from that of the patients enrolled in the 2 landmark studies with HCV genotype 4 being the predominant etiologic factor in the Egyptian population compared to HCV genotype 2 and 3 in the European population of SHARP study or HBV infection in the Asian pacific study [2,3]. Thus, a study of the efficacy and safety of sorafenib in an unselected Egyptian HCC population was warranted. So, in the current study we evaluated sorafenib monotherapy in the everyday clinical practice patient population as they present in Egypt. Furthermore we explore the role of a number of baseline clinicalopathological parameters in treatment evaluation and its association to survival outcome.

Patients and methods

Patients

Access to sorafenib was made available at Ain Shams University Hospitals, clinical oncology department since 2010. All patients considered for sorafenib were reviewed by a panel of clinical oncologists. The criteria for the selection of patients for sorafenib monotherapy were: advanced hepatocellular carcinoma diagnosed according to the criteria of AASLD [6], not amendable for locoregional treatment (including transcatheter arterial chemoembolization, radio frequency ablation (RFA), and surgery), ECOG PS 0–2, Child Pugh A or B with no history of uncontrolled cardio- or cerebrovascular disease. All patients had a dynamic imaging study (three-phase CT scan or MRI) performed at baseline, blood pressure assessment, blood workup including complete blood count, liver function tests, coagulation studies and serum $\alpha$FP.

Treatment

Sorafenib was administered at a dose of 800 mg daily. Dose reduction and treatment delay were performed as per the seminal phase 2 study of sorafenib in HCC. Treatment was continued until radiological progression, unacceptable toxicity, or death. Patients were seen every 3 weeks for clinical assessment. Response assessment was performed every 2 months and included repeating the initial dynamic imaging study (CT-scan or MRI), liver function tests, coagulation studies and serum $\alpha$FP.

Efficacy and toxicity assessment

Response evaluation was performed according to RECIST criteria, v.1.0 while toxicity assessment was performed according to NCI-CTCAE v3.0 [7].

Statistical analysis

The primary end points were overall survival (OS) while secondary end points included progression free survival (PFS) and toxicity. The analysis of objective tumor response was performed according to an intention to treat analysis (ITT). The Kaplan–Meier method was used for the survival analysis. A Cox proportional hazard analysis of baseline clinicopathological characteristics was performed to assess a potential association to survival outcome and followed by a multivariate Cox regression analysis. The level of statistical significance was 5%. All P values are two sided and reported with 95% confidence intervals. All statistical analyses were carried out using SPSS v.17 software.

Results

Patient characteristics

A total of 41 patients were consecutively treated at the Department of clinical Oncology at Ain Shams University Hospitals, Cairo, Egypt between January 2010 and June 2011 and followed until January 2012. Median follow-up time was 13 months, ranging from 30 to 777 days.

Table 1 shows baseline patient and disease characteristics together with the results of the univariate survival analysis of potential prognostic factors. 53 percent of the patients were in PS 0–1, and 30% had a well preserved liver function (CP-A). HCV was the primary cause of liver disease, followed by
non alcoholic steatohepatitis. A large proportion of patients had highly advanced disease with macroscopic vascular invasion (38%) and extrahepatic metastases (23%) (Table 2).

### Treatment outcome

The median OS (mOS) for the entire cohort of patients was 6.25 months. As illustrated in Fig. 1, patients in PS 1 had a mOS of 7.01 months, whereas patients in PS 2 had a mOS of 3.03 months ($p = 0.0001$). CP-A patients had a mOS of 12.04 months versus 5.23 months among CP-B patients ($p = 0.013$).

The median PFS (mPFS) for the entire cohort of patients was 4.0 months, patients with PS 1 had a mPFS of 5.8 months, whereas patients in PS 2 had a mPFS of 2.2 months ($p = 0.001$). CP-A patients had a mPFS of 8.0 months versus 4.0 months among CP-B patients ($p = 0.007$).

Besides PS and Child–Pugh status, baseline alpha feto-protein levels had a significant influence on survival in the multivariate analysis. Thirty-four percent of the patients did not receive a full dose of sorafenib, because of dose reduction during treatment. Discontinuation of treatment was due to objective disease progression in 85% of patients, while 15% stopped sorafenib therapy due to specific adverse event. Two patients died while on treatment, all of them due to disease progression. Three patients were still on treatment at the end of follow up. Thirty-eight patients (92%) completed at least 12 weeks of sorafenib therapy and were evaluable for the assessment of tumor response according to the definition sited above. There was one case of complete response. Eleven percent had a partial response with substantial regression of tumor lesions on the CT scan. All responders were in PS 0–1 at baseline, and 5 of the total 7 were classified as CP-A.

### Toxicity

Twenty-three percent of the patients experienced grade 3–4 toxicity, with the most frequent being fatigue, diarrhea, and hand-foot syndrome. (Table 3)

### Discussion

Hepatocellular carcinoma has increased in Egypt in the past years, becoming the most common cancer among men [8]. Despite significant progress with the advent of Sorafenib as a treatment option for advanced HCC, advanced HCC is still challenging for every practicing oncologist. In this retrospective analysis of Sorafenib-treated Egyptian HCC patients, we found a median overall survival of only 6.25 months (Figs. 2 and 3).
This survival rate is lower than that in the landmark SHARP study (10.7 months), and also in the Asian-Pacific study (6.5 months) [2,3]. We found that the prognosis was dependent on performance status, Child Pugh status in addition to baseline alpha fetoprotein. Patients with a better performance and a healthier liver condition lived almost twice as long as the less healthy subjects, but still not as long as the patients in the landmark phase 3 sorafenib studies. This may be explained by the difference in baseline clinicopathological characteristics of the patients reviewed in our study compared to the patients randomized in the SHARP and Asian-Pacific trials. In our study, a large percentage of our patients were in PS 2 and child score >7. Moreover, the etiology of underlying liver disease is different with the majority of patients in our study having post hepatitis C liver cirrhosis, whereas only about 5% have non alcoholic steatohepatitis. Patients with HCC and an underlying hepatitis C related liver cirrhosis may be particularly subject to co morbidity which will influence the tolerability of sorafenib. Therefore, one third of the patients did not receive a full dose of sorafenib.

A more recent, prospective series of 300 patients classified as CP-A or -B treated with sorafenib reported a median OS for child B patients of 3.4 months, which is lower than the survival rate we found in this study (mOS of 5.2 months for CP-B patients) [9]. Moreover, three subjects in our study turned out to be long-term survivors and continued treatment at the end of follow up, suggesting that some patients may derive exceptional benefit from sorafenib, and one subject in our study has achieved complete response consistent with other published case reports of complete responders in the literature [10,11]. Therefore, reliable predictive factors—both clinical and molecular—enabling the identification of this subset of patients are eagerly awaited. Alpha-fetoprotein (αFP), a traditional tumor marker of HCC, has been suggested previously as a marker for response to sorafenib [12]. In agreement with other clinical studies we found that higher baseline αFP was an independent poor prognostic indicator [13].

As demonstrated in other reports [14], sorafenib is also tolerable in those with compromised liver function or PS as the incidence and grade of adverse events were not different significantly among the patients with better versus worse performance or child score. However, the pattern of side effects is different with higher incidence of hepatotoxicity in those with higher baseline child score, additionally it should be noted that child B and poor performance patients received sorafenib for a shorter time with higher incidence for dose reduction and/or discontinuation.

Treatment with sorafenib has been deemed cost effective compared with best supportive care in hepatocellular carcinoma in some developed countries, however in a developing country like Egypt cost effectiveness and cost utility analysis need more detailed assessment [15]. In conclusion, sorafenib treatment is tolerable and associated with clinical benefit in Egyptian patients with advanced HCC with good performance PS and compensated liver function. The outcome of patients with poor performance or compromised liver function is poor, regardless of whether they are treated or not. Therefore, in the context of a low income country like Egypt, sorafenib treatment cannot be recommended except for a highly selected subgroup of patients with better performance and liver function. Further molecular and clinical assessment of the distinct pathobiological pattern of HCC in Egypt is highly recommended to further elucidate the nature of disease in this area of the world.
Conflict of interest

None declared.

References

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