A Clinical Phase II Study of Sorafenib in Advanced Hepatocellular Carcinoma
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Abstract

Purpose: Sorafenib is an oral multikinase inhibitor of the vascular endothelial growth factor receptor, the
platelet-derived growth factor receptor and Raf with demonstrated efficacy as first-line therapy for patients
with inoperable hepatocellular carcinoma (HCC). We reported the preliminary results of this treatment to evaluate its
safety, tolerability, and efficacy in patients with inoperable HCC.

Patients and Methods: Patients with inoperable HCC and a Karnofsky performance status (KPS) of ≥70, Child-
Pugh (CP) score of A or B, an elevated alphafetoprotein (AFP) level and adequate hematologic, renal and hepatic
functions; were enrolled. No Prior therapy was permitted. The regimen was sorafenib at a dose of 400 mg bid, given
7 days per week. Treatment was maintained until disease progression or unacceptable toxicity.

Results: Twenty one patients with a median age of 53 years (range, 39-73 years) were accrued at Clinical
Oncology Department, Faculty of Medicine, Tanta University Hospital, Egypt and King Abd-Elaziz Hospital, Gedah,
KSA. Previously, no Prior therapy was permitted. All patients who were entered on the study were assessable for
toxicity and response of sorafenib. There were 2 clinical responses (9.5%) and another 8 (38.1%) had stable disease.
Disease control rate was 47.6%. No Grade 3-4 hematologic toxicities were recorded. The most common grade 3-4
non-hematological toxicities were fatigue in 3 patients (14.3%), hand-foot skin reaction (HFS) in 2 patients (9.5%)
and Diarrhea in 2 patients (9.5%). The estimated median progression-free and median overall survival times were 4
and 9 months, respectively, and the 1-year overall survival rate was 38.1%. There was no treatment-related death.

Conclusion: The results of this study suggested that, in the population with inoperable HCC, daily sorafenib
regimen had good clinical activity with an acceptable toxicity.

Keywords: Hepatocellular carcinoma; Inoperable hepatocellular carcinoma; Targeted therapeutic; Chemotherapy; Daily sorafenib

Introduction

Effective treatment for hepatocellular carcinoma (HCC) is desperately needed because it is a deadly disease whose worldwide
annual incidence matches its prevalence and is the fifth leading cause of cancer death worldwide [1]. The mainstay of management of HCC
is early diagnosis with the hope of applying curative therapy. It is estimated that with the application of current surveillance modalities,
only, 30%-40% of cases could be diagnosed early enough for curative treatments [2].

Given the limited efficacy of adjuvant and palliative treatment options to date, there has been an extensive effort to identify other
agents useful for the management of HCC. Systemic chemotherapy has largely been disappointing in terms of palliation or cure. Cytotoxic
chemotherapy has been shown to provide no survival benefit [3].

Sorafenib, a tyrosine-kinase inhibitor, is widely used in the treatment of advanced hepatocellular carcinoma. In 2007, Llovet and colleagues first reported the results of the international, phase III, placebo-controlled Sorafenib HCC Assessment Randomized Protocol
(SHARP) trial, which demonstrated a longer overall survival (OS) time and time to tumor progression (TTP), compared to placebo in patients
with advanced hepatocellular carcinoma (HCC) [4]. The median OS time was 10.7 months in the sorafenib group and 7.9 months in the
placebo group. The median TTP was 5.5 months in the sorafenib group and 2.8 months in the placebo group. In a subsequent randomized
phase III study conducted in Asia, sorafenib also demonstrated a longer OS and TTP in patients with advanced HCC [5]. These studies have led to the timely approval of sorafenib in HCC in many countries worldwide.

The development of sorafenib in HCC has several important implications. First, it validates the use of molecularly targeted agents
in HCC. Second, it sets a new standard for ongoing and future clinical trials in advanced HCC.

Therefore, we designed this trial to evaluate the preliminary results of daily sorafenib given as a single agent at doses of 400 mg bid, given
7 days per week in patients with inoperable HCC. The objectives of the current trial were to evaluate the response rate, toxicity, and survival
of patients who were treated with this dose and schedule of sorafenib.

Materials and Methods

Patients

Between May 2009 and April 2011, 21 patients over the age of 18 years with newly diagnosed, histologically confirmed, inoperable
HCC, were the subjects of this study. All patients were assessable for response at Clinical Oncology Department, Faculty of Medicine, Tanta
University Hospital, Egypt or King Abd-Elaziz Hospital, Gedah, KSA. Patients were required to have a KPS of ≥70, Child-Pugh (CP) score of

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Received November 19, 2011; Accepted January 10, 2012; Published January
15, 2012

Citation: El Deen HSG, Sadaka EAE (2012) A Clinical Phase II Study of Sorafenib
in Advanced Hepatocellular Carcinoma. Anaplastology 1:101. doi: 10.4172/2161-
1173.1000101

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A or B, elevated alphafetoprotein (AFP) level and adequate hematologic, renal, and hepatic functions. Eligible patients were also required to have no lack of physical integrity of the upper gastrointestinal tract or any medical condition that could interfere with the oral administration of sorafenib and had not received previous therapy for HCC.

Exclusion criteria included patients with tumors of mixed histology or fibrolamellar variant, pregnant or lactating women. In addition patients who required intravenous or enteral nutrition because of a poor performance status and malnutrition or patients with any previous or concurrent malignancies at other sites were also considered ineligible.

Study design and treatment

This was single-arm and multicenter, international, phase II clinical trial in advanced HCC patients. The Ethics Committee granted protocol approval and all patients signed an informed consent before the initiation of any treatment.

We assigned eligible patients to receive sorafenib (marketed as Nexavar) at a dose of 400 mg bid, given 7 days per week. Treatment was maintained until disease progression or unacceptable toxicity. Before the initiation of any treatment.

Toxicity evaluation

We analyzed adverse events during the entire study period. The primary endpoints of this study were tumor response and toxicity. Other study objectives were the time to disease progression, which was defined as the time between start of therapy and the date of the first documented progression of disease or death, and overall survival, which was defined as the time between the date of start of therapy and the date of death or last follow up according to the Kaplan-Meier method [8] with SPSS [Statistical package] (version 12).

Results

Patient characteristics

A total of 21 consecutive patients with newly diagnosed, histologically confirmed, inoperable HCC, treated at Clinical Oncology Department, Faculty of Medicine, Tanta University, Egypt and King Abd-Elaziz Hospital, Gedah, KSA were enrolled in this phase II trial from May 2009 to April 2011. The patient characteristics of all enrolled patients are listed in Table 2. The median age of study participants was 53 years (range, 39-73 years), 71.4% of who were male. At time of study entry, most of the patients (90.5%) had a KPS of ≤ 80%. Median time between primary diagnosis of advanced HCC and inclusion was 2 months (range, 1-8 months). The tumor was multifocal in 71.4% with a median tumor size of 8 cm (range, 3-11 cm). Portal vein thrombosis was present in 76.2% of patients. Two patients were still receiving treatment as of September 30, 2011. Sixty-two percent had hepatitis B and 85.7% had hepatitis C, while 66.7% had Child-Pugh (CP) score A and 33.3% had CP score B.

Survival

The Median progression-free survival (PFS) and overall survival (OS) times were 4 months and 9 months respectively and the 1-year OS rate was 38.1% (Table 3).

Toxicity

We analyzed adverse events during the entire study period. The major Grade 3/4 adverse reactions to this regimen are listed in Table 4. No treatment-related mortality was noted in this cohort. Most of the drug-related toxicities were mild and manageable. Hand-foot skin reaction (HFS), a frequent side effect of sorafenib, was the most common treatment-related adverse event, occurring in 61.9% (13/21) of patients. The majority of HFS was mild to moderate. Grade 3/4 HFS occurred in only 2 patients (9.5%). Diarrhea was experienced by 10 patients (47.6%), but at grade 3/4 intensity in only 2 patients (9.5%).
A total of 602 patients with advanced-stage HCC who were not candidates for, or who had disease progression after locoregional therapy, were enrolled in the Sorafenib HCC Assessment Randomized Protocol (SHARP) trial [4]. The 1-year survival for the sorafenib group was 44% and 33% for the placebo group. The median survival for the sorafenib group was 10.7 months from enrollment compared to 7.9 months for those who received placebo. There were no complete responses in the study. This phase 3 clinical trial was stopped early at its second interim analysis because of the evidence for a survival benefit associated with sorafenib therapy and has been subsequently approved by the U.S. Food and Drug Administration.

However, in our study, the disease control rate of 47.6%, the median progression-free survival of 4 months, the median overall survival of 9 months and the 1-year overall survival rate of 38.1%, were comparable with that reported in a phase II study of sorafenib in patients with advanced HCC, carried out by Abou-Alfa et al. [6] in which the estimated median OS and PFS were 9.2 months and 4.2 months respectively. While it was lower than that reported in Llovet et al. [4] study for the sorafenib group in which the 1-year OS rate was 44% and the estimated median OS and PFS were 10.7 months and 5.5 months respectively. There are three possible explanations. First, five patients died before the first evaluation due to rapid disease progression. Usually, patients with life expectancy, 3 months will not be included in clinical trials. But, this may be representative for our daily practice in inoperable HCC instead of selection bias for production a good response phase II trial. Secondly, a higher percentage of relative poor performance was presented in this study population. Ninety percent of our patients had a KPS of ≤80%; many studies demonstrated significantly higher risk of death in patients with low performance status [15-17]. Thirdly, the differences in study designs and the low number of our patients as a result of cost which limit widespread use of sorafenib in our country with limited resources may be the main reasons why this trial achieved lower results than randomized phase III trial by Llovet et al. [4].

In our study, the toxicity profile of this regimen was excellent, with no Grade 3-4 hematologic toxicities. Hand-foot skin reaction, diarrhea and fatigue were the most commonly reported Grade 3/4 toxicities. The frequency of these toxicities was somewhat higher than previously reported in other study with daily administration of sorafenib [6], probably because of the poor initial performance status of the study population and their poor nutritional status. In addition, the low number of patients in our study constitutes the main reason for this difference.

In conclusion, this is the first report of results of daily administration of sorafenib in the treatment of inoperable HCC in both, Clinical Oncology Department, Tanta University Hospital, Faculty of Medicine, Tanta University, Egypt and King Abd-Elaziz Hospital, Gedah, KSA. The preliminary results of this study demonstrated that daily administration of sorafenib, is a promising agent for patients with inoperable HCC and we propose it as an alternative approach for inoperable HCC that has been the most investigated is doxorubicin (adriamycin) [10-12]. A systematic review published in 1997 found only 10 randomized clinical trials evaluating chemotherapy for HCC, nine of which involved doxorubicin [13]. The only study that compared doxorubicin to no treatment showed no benefit [13]. In the other studies, doxorubicin was not shown to be better than any of the other agents tested with the exception of 5-fluorouracil monotherapy, which showed an improved median survival of 14 versus 6 weeks for doxorubicin [13]. Nevertheless, doxorubicin has continued to be used as a control arm in other studies with published median OS times between 3.7 and 8.8 months with no clear survival benefit [3].

A meta-analysis of seven randomized controlled trials comparing tamoxifen to placebo failed to show a difference in 1-year survival (23% versus 22%) [14]. In our study, the median PFS was 4 months, and the median OS was 9 months. These results are somewhat higher than other consistently reported results from other chemotherapy regimens, including single-agent 5-FU. The current results suggest that the daily administration of sorafenib is an active and safe agent for patients with inoperable HCC.

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![Table 3: Overall Survival and PFS of All Patients with Advanced HCC (n =21).](image)

### Table 3: Overall Survival and PFS of All Patients with Advanced HCC (n =21).

| Variable                  | Survival       |
|---------------------------|----------------|
| Overall Survival (months) |               |
| Median                    | 9.00 months    |
| 6-month                   | 57.1%          |
| 12-month                  | 38.1%          |
| Progression-free survival (months) |       |
| Median                    | 4.00 months    |
| 6-month                   | 28.6%          |
| 12-month                  | 9.9%           |

### Table 4: Grade3/4 Treatment-Related toxicity among all patients (N = 21 patients).

| Toxicity                  | No. | %  |
|---------------------------|-----|----|
| Fatigue                   | 3   | 14.3|
| Hand-foot skin reaction   | 2   | 9.5 |
| Diarrhea                  | 2   | 9.5 |
| Nausea/vomiting           | 1   | 4.8 |

Other grade 3/4 toxicities observed were fatigue (14.3%), and nausea/vomiting (4.8%). All patients remained outpatients throughout the treatment period.

### Discussion

In the current study, the daily administration of sorafenib in patients with newly diagnosed, histologically confirmed, inoperable HCC, was associated with a 47.6% disease control rate and a median overall survival of 9 months. Although several Phase II and Phase III trials previously reported activity of sorafenib as a single agent in patients with inoperable HCC [4-6], to our knowledge, this is the first study in patients with inoperable HCC in which this agent was administered in Egypt and KSA. Treatment schedules and doses were selected based on other previous studies [4,6,9].

Other agents that are used in the treatment of patients with inoperable HCC that has been the most investigated is doxorubicin (adriamycin) [10-12]. A systematic review published in 1997 found only 10 randomized clinical trials evaluating chemotherapy for HCC, nine of which involved doxorubicin [13]. The only study that compared doxorubicin to no treatment showed no benefit [13]. In the other studies, doxorubicin was not shown to be better than any of the other agents tested with the exception of 5-fluorouracil monotherapy, which showed an improved median survival of 14 versus 6 weeks for doxorubicin [13]. Nevertheless, doxorubicin has continued to be used as a control arm in other studies with published median OS times between 3.7 and 8.8 months with no clear survival benefit [3].

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Its second interim analysis because of the evidence for a survival benefit associated with sorafenib therapy and has been subsequently approved by the U.S. Food and Drug Administration.

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