Expansion of Palliative Care in the Gulf Area
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Can we use Sorafenib for advanced Hepatocellular Carcinoma (HCC) Child Pugh B?

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Abstract

HCC is the third cause of cancer-related death worldwide and the fifth most common cancer in the world with an increasing incidence in some areas like Europe, USA and the Gulf region. In this study patients with advanced HCC in both group child pugh A and B were treated with sorafenib.

Methods:

This is a retrospective observational study to assess the safety and effectiveness of sorafenib in patients with advanced HCC child pugh A and B who failed local palliative ablation therapy or were not eligible for such therapy. Forty six patients included.

Results:

In both child pugh A and B group the sorafenib was well tolerated and survival was improved but it was more pronounced in the child pugh A group.

Conclusion:

This is the first study that includes high percentage (47%) of child B group to be treated with sorafenib. Compared with international data there was improved overall survival in both groups.

Key words:

Hepatocellular carcinoma, sorafenib, hepatitis C virus, hepatitis B virus

Introduction

Hepatocellular carcinoma (HCC) is an aggressive tumor accounting for more than 626,000 new cases per year worldwide (1). It has significant mortality because it is often diagnosed late in its course. It is the third cause of cancer related death worldwide and the fifth most common cancer in the world with an increasing incidence in some areas like Europe, USA and the Gulf region (2). HCC generally develops in the context of chronic liver disease and cirrhosis (3). In the Middle East chronic liver disease is secondary to hepatitis C (HCV) & B (HBV) are the commonest (4). In contrast to USA where alcoholic liver disease is the most common (5), HCC is a heterogeneous disease in terms of etiology as well as clinical presentation and behavior, both the extent of the liver impairment and the advanced tumor state upon diagnosis make the standard treatment with surgical resection difficult, with median survival of 6 to 20 months (6).

Methods

This is a retrospective observational study to assess the safety and effectiveness of sorafenib in patients with advanced HCC who failed local palliative ablation therapy or were not eligible for such therapy. Patients included have been diagnosed with HCC from year 2008 to year 2013. Diagnosis was made by diagnostic radiological imaging criteria either MRI with gadolinum or CT with contrast, few patients required histological confirmation for the diagnosis. All patients were classified according to Child-pugh classification and most of them had chronic liver disease either secondary to hepatitis C or B. The study population consisted of 46 patients with advanced stage of hepatocellular carcinoma. According to Child Pugh Classification, 24 patients were class A and 22 patients class B. 6 patients had liver transplant 4 of them had the transplant for localized HCC then relapsed and treated with sorafenib. Patients have been treated with sorafenib with total oral dose of 800mg/day divided in two daily doses. Around 61% of the patients (28 patients) tolerated...
the Sorafenib very well, the remaining patients required dose reduction because of side effects as severe diarrhea, hand foot syndrome and elevated liver enzyme and bilirubin. Six patients have skin rash, 9 have diarrhea and 1 patient stopped treatment because of significant liver impairment.

Results

Our study is a retrospective observational study and we evaluated patients from May 2008 to December 2013 treated with sorafenib. Data from the total of 48 patients were analyzed, 43 (90%) were males and 5 (10%) were females. Forty-two patients (88%) were non-Qatari and 6 (12%) were Qatari. 46 patients we assessed for survival, 2 patients have insufficient data for assessment. 14 patients lost their follow up (either travelled to their countries or other reasons). Majority of patients received the recommended 800 mg daily dose of sorafenib for both Child-Pugh A (52%) and B (48%). However, the duration of treatment tended to be less for patients with Child-Pugh B. The adverse effects were mainly fatigue, gastrointestinal and dermatological (Table 1). The median overall survival for child-Pugh A was 21.7 months (95% confidence interval 13.1-30.3) and for Child-Pugh B was 9.2 (95% confidence interval 6.7-11.7) with significant difference between the 2 group P value 0.003. Figure (1)

Sorafenib was well tolerated by most of the patients in both Child-Pugh classes with significant improved overall survival, although overall survival was slightly shorter in patients with Child-Pugh B.

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Number of patients</th>
<th>Grade 1,2</th>
<th>Grade 3,4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>10</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>GI symptom</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>9</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Dermatologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>6</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>HFS</td>
<td>4</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Pruritic</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>LFT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase bilirubin</td>
<td>6</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Elevated liver enzyme</td>
<td></td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Liver failure</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 1. Adverse effects of Sorafenib

Discussion

Unresectable HCC is a challenge to manage, giving the multiple co-morbidities present in these patients. Local treatment options such as trans-arterial chemoembolization (TACE) or radiofrequency ablation (RFA) are not effective for all patients and associated with high recurrence rate (7), making systemic therapy the alternative option for treatment with the new targeted therapy superior to chemotherapy alone in term of overall survival and tolerability (8).

Sorafenib is a multi-targeted tyrosine kinase inhibitor against Vascular Endothelial Growth Factor Receptor (VEGFR 1, 2 and 3) and Platelet-derived Growth Factor Receptor β (PDGFR β) that inhibit tumor angiogenesis (9). Sorafenib has been reported initially in 2007 as a systemic targeted therapy approved for treatment of advanced cases of hepatocellular carcinoma with significant survival benefit over palliative care alone.
Patients with unresectable advanced HCC treated with sorafenib have been evaluated in two studies (SHARP and Asia-Pacific). Both phase III studies demonstrated significant improvement in overall survival in these patients with the use of sorafenib. Majority of patients evaluated in both studies were Child-Pugh A\(^8\). In the SHARP study the median overall survival was 10.7 months in the group of patient received sorafenib which are mainly child-Pugh A while in the Asian-Pacific study was 6.5 months and in our study the median overall survival for child-Pugh A was 21.7 months (95% confidence interval 13.1-30.3) and for Child-Pugh B was 9.2 (95% confidence interval 6.7-11.7) with significant difference between the 2 group P value 0.003. Figure (1)

In general clinical trials in HCC include only patients with preserved liver function, as severe liver dysfunction associated with Child-Pugh B or Child-Pugh C status represents a competing cause of death and may confound results\(^{11}\). Child-Pugh B patients with advanced HCC have been evaluated in GIDEON prospective study

In this study we have evaluated patients with advanced HCC who received sorafenib as systemic therapy between years 2008 – 2013 at our facility in NCCCR - Qatar. We have included patients with Child-Pugh class A and B. Sorafenib was well tolerated by most of the patients in both Child-Pugh classes, the main adverse effect were fatigue, gastrointestinal and dermatological. Compared with international data we have significant improved overall survival, although overall survival was shorter in patients with Child-Pugh B as expected.

**Conclusion**

Sorafenib can be used for treatment of advanced HCC child-Pugh B with good tolerability, but survival was shorter for patient with child-pugh B disease. We need a larger study group to prove the efficacy of this small sample study.

**References**

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