Meta-analysis of the Efficacy of Sorafenib for Hepatocellular Carcinoma

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Abstract

Purpose: By carrying out a meta-analysis of randomized controlled trials that compared sorafenib or combined chemotherapy with placebo or combined chemotherapy, the effectiveness of sorafenib in hepatocellular carcinoma was evaluated in the present study, which also provided clinical practice guidelines of evidence-based-medicine. Methods: We reviewed PubMed citations concerning sorafenib treating hepatocellular carcinoma in randomized controlled trials from Jan 2000 to July 2012. All the literature was extracted by Cochrane systematic reviews and underwent meta-analysis with RevMan 5.0 software. Results: Finally, four papers documenting randomized controlled studies were included. Compared with controls, sorafenib was shown to significantly increase overall survival (OS), time to progression (TTP), and disease control rates (DCR), but not the time to symptom progression (TTSP) in hepatocellular carcinoma patients. The incidence of grade-III/IV adverse reactions, including hand-foot-skin reactions, diarrhea, hypertension and skin rash or desquamation, in sorafenib treatment group was higher than that in controls. However, there was no significant difference in the incidence of hypodynamia between the two groups. Conclusions: Sorafenib exerts significant curative effects in hepatocellular carcinoma.

Keywords: Sorafenib - tyrosine kinase inhibitor - VEGF receptor - HCC - meta-analysis

Introduction

Hepatocellular carcinoma (HCC, also called malignant hepatoma), ranking 3rd following gastric carcinoma and esophageal carcinoma, is one of the most common types of cancer around the world. Every year more than 1 million new cases added (Parkin et al., 2008). Hepatocellular carcinoma with high malignant degree progresses rapidly so that diagnosis timely appears to be of essence. The treatment of advanced hepatocellular carcinoma is quite tough, and there is no standard therapeutic protocol. Hepatocellular carcinoma with poor prognosis and short survival time is a severe challenge for clinical medicine (Jemal et al., 2005).

Vascular endothelial growth factor (VEGF)-targeted therapies have become a cornerstone in the treatment of many cancers. They have shown to improve clinical outcomes in several malignancies and are widely used. Sorafenib (commercial name Nexavar) is an FDA-approved VEGF receptor (VEGFR) tyrosine kinase (TK) inhibitor (TKI) in advanced renal cell cancer (RCC) and hepatocellular carcinoma (HCC) and the first-in-class drug to be approved in December 2005 (Llovet et al., 2008; Cheng et al., 2009; Escudier et al., 2009). Sorafenib is an oral multikinase inhibitor targeting the intracellular TK domain of the VEGFR, as well as several other TK such as platelet derived growth factor receptor (PDGFR), stem cell factor KIT receptor, RET and FLT-3, blocking the downstream signaling and exerting anti-angiogenic, anti-proliferative and pro-apoptotic effects and inhibiting tumor angiogenesis. Sorafenib is also unique in targeting the Raf/Mek/Erk pathway (MAP Kinase pathway) (Liu et al., 2006; Wilhelm et al., 2006). Moreover, these receptors of kinase usually overexpress in hepatocellular carcinoma patients (Villanueva et al., 2007) and several clinical studies have been confirmed that sorafenib is able to effectively extend life time of these patients (Dal Lago et al., 2008, Furuse et al., 2008).

In this paper, we applied the principle and method of evidence-based medicine to gain literatures on sorafenib treating hepatocellular carcinoma in randomized controlled trials, whose quality were evaluated and screened. Base on meta-analysis of these cases, the efficacy of sorafenib in hepatocellular carcinoma were assessed, which provided clinical practice guidelines of evidence-based-medicine.
Table 1. General Characteristic of the Four Eligible Literatures/trials Involved

<table>
<thead>
<tr>
<th>Research</th>
<th>Patients</th>
<th>Cases</th>
<th>Ages</th>
<th>Hepatic function</th>
<th>Therapeutic regime</th>
<th>Male/Female ratio</th>
<th>Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Llovet JM 2008</td>
<td>Europe, America, Oceania</td>
<td>299/303</td>
<td>64/96/63</td>
<td>95/98</td>
<td>Sorafenib 400 mg, bid.</td>
<td>87:13/87:13</td>
<td>OS, TTP, TTSP, DCR, adverse reaction</td>
</tr>
<tr>
<td>Cheng AL 2009</td>
<td>Asian-Pacific region</td>
<td>150/76</td>
<td>51/52</td>
<td>97/97</td>
<td>Sorafenib 400 mg, bid.</td>
<td>85:15/87:13</td>
<td>OS, TTP, TTSP, DCR, adverse reaction</td>
</tr>
<tr>
<td>Abou-Alfa GK 2010</td>
<td>Several nations</td>
<td>47/49</td>
<td>66/65</td>
<td>100/95.9</td>
<td>Placebo 400 mg, bid.</td>
<td>66:34/85:7.1:3.3</td>
<td>OS, TTP, adverse reaction</td>
</tr>
<tr>
<td>Kudo M 2011</td>
<td>Japan, Korea</td>
<td>229/229</td>
<td>69/70</td>
<td>--</td>
<td>Sorafenib 400 mg, bid.</td>
<td>76:24/73:4.26:4</td>
<td>OS, TTP, adverse reaction</td>
</tr>
</tbody>
</table>

*sorafenib group/control group; ^bid, twice a day; **qd, once a day

<table>
<thead>
<tr>
<th>Research</th>
<th>Therapeutic regime</th>
<th>Neutral OS and TTP (95%CI)</th>
<th>P value</th>
<th>Neutral TTSP (95%CI)</th>
<th>P value</th>
<th>Neutral TTSP (95%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Llovet JM 2008</td>
<td>Sorafenib</td>
<td>10.7 (9.4-13.3)</td>
<td>&lt;0.001</td>
<td>5.5 (4.1-6.9)</td>
<td>&lt;0.001</td>
<td>4.1 (-)</td>
<td>0.77</td>
</tr>
<tr>
<td>Cheng AL 2009</td>
<td>Sorafenib</td>
<td>6.5 (5.6-7.6)</td>
<td>0.014</td>
<td>2.8 (2.6-3.6)</td>
<td>0.0005</td>
<td>3.5 (2.8-4.24)</td>
<td>0.5</td>
</tr>
<tr>
<td>Abou-Alfa GK 2010</td>
<td>Doxorubicine + sorafenib</td>
<td>-</td>
<td>-</td>
<td>6.4 (4.8-9.2)</td>
<td>0.02</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Kudo M 2011</td>
<td>Sorafenib</td>
<td>13.7 (8.9-NA)</td>
<td>0.006</td>
<td>7.2 (5.6-9.1)</td>
<td>0.049</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Placebo</td>
<td>6.5 (4.5-9.9)</td>
<td>5.3 (3.8-5.6)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Eligible trials

Our search yielded 590 potentially relevant trials in total. After checking their titles and abstracts, 580 were excluded due to reviews, basic researches, case reports, observational studies, retrospective studies or non-randomized controlled clinical trials. Then, we carefully screened each one of the remaining 10 randomized controlled clinical trials, and excluded another 6, which were uncompleted phase 3 clinical trials or irrelevant to the use of sorafenib in hepatocellular carcinoma. Finally, we identified four randomized trials with sorafenib, published in English, as eligible for inclusion in the meta-analysis as shown in Table 1 (Llovet et al., 2008; Cheng et al., 2009; Abou-Alfa et al., 2010; Kudo et al., 2011). All trials included in this analysis were double-blind placebo-controlled randomized phase 3 clinical trials. Patients in these reports came from several states and regions, and sorafenib was administrated alone or with cytotoxic chemotherapeutic agent doxorubicine. The dosage and schedule of sorafenib was the currently FDA-approved one (400 mg PO twice daily) in each trial.

Efficacy of Sorafenib in Hepatocellular Carcinoma

The four literatures reported time to progression (TTP); three of them reported Overall survival (OS) and Time to symptomatic progression (TTSP); two reported Disease Control Rate (DCR).
observed (hepatocellular carcinoma patients. Heterogeneity was not observed (P=0.09), and the pooled estimate calculated based on the fixed-effects model. Meta analysis suggested that sorafenib could improve DCR of hepatocellular carcinoma patients (RR=1.62, 95% CI 1.00 - 2.64; P=0.05) (Figure 1).

Analysis of grade-III/IV adverse reactions in sorafenib treated hepatocellular carcinoma patients

Reported grade-III/IV adverse reactions in these four literatures included hand-foot-skin reactions, hypodynamia, hypertension and skin rash or desquamation. All of them reported hand-foot-skin reactions, diarrhea, hypertension and skin rash or desquamation in hepatocellular carcinoma patients, while three reported hypodynamia.

Hand-foot-skin reactions

Four papers reported hand-foot-skin reactions in hepatocellular carcinoma patients. Heterogeneity was not observed (P=0.70), and the pooled estimate calculated based on the fixed-effects model. Meta analysis showed the incidence in sorafenib group was higher than that in control (RR=1.44, 95% CI 1.00 - 2.00; P=0.05) (Figure 2A).

Hypodynamia

Three papers mentioned hypodynamia occurrence. Heterogeneity was not observed (P=0.80), and the pooled estimate calculated based on the fixed-effects model. Meta analysis indicated there was no significant differences between sorafenib group and the control (RR=1.44, 95% CI 0.56 - 3.73; P=0.45) (Figure 2B).

Diarrhea

All the four papers presented diarrhea occurrence in hepatocellular carcinoma patients. Heterogeneity was not observed (P=0.38), and the pooled estimate calculated
based on the fixed-effects model. Meta analysis revealed higher incidence in sorafenib group (RR=3.37, 95% CI 1.49 - 7.66; P=0.004) (Figure 3A).

**Hypertension**

All the four papers showed the incidence of hypertension. Heterogeneity was not observed (P=0.86), and the pooled estimate calculated based on the fixed-effects model. Meta analysis showed that there was no significant differences between sorafenib group and the control (RR=3.51, 95%CI 0.88 - 14.09; P=0.08) (Figure 3B).

**Skin rash or desquamation**

All the four papers presented occurance of skin rash or desquamation in hepatocellular carcinoma patients. Heterogeneity was not observed (P=0.77), and the pooled estimate calculated based on the fixed-effects model. Meta analysis indicated higher incidence in sorafenib group (RR=5.86, 95%CI 1.39 - 24.72; P=0.02) (Figure 4).

**Discussion**

Sorafenib is a multikinase inhibitors, targeting to the serine-threonine kinase and receptor protein tyrosine kinases (RPTKs) in tumor cells and tumor blood vessels. It was used in renal cell carcinoma first, which prolongs neutral progression free survival time from 2.8 months to 5.5 months (Escudier et al., 2007). Based on further investigation, sorafenib improves the survival of patients with advanced hepatocellular carcinoma (HCC) (Huitzil-Melendez et al., 2008; Chen et al., 2011). In the present paper, OS, TTP, TTSP, DCR and adverse reactions in clinical randomized controlled trials were summarized and assessed to confirm the efficacy of sorafenib in HCC therapy, providing clinical practice guidelines of evidence-based-medicine.

Results in this analysis showed efficacy of sorafenib treating HCC was obvious, in prolonging OS and TTP and increasing DCR. Thus there was no significant difference in prolonging TTSP. The incidence of grade-III/IV adverse reactions, including hand-foot-skin reactions, diarrhea, hypertension and skin rash or desquamation, in sorafenib treatment group was higher than that in control group. Thus there was no significant difference in the incidence of hypodynamia between the two groups.

Studies involved in this meta-analysis were all multicentre trials. HCC patients were from several regions and states and blinding method and randomized method were scientifically applied, which makes these data reliable. Nevertheless, despite the size of this meta-analysis, there may be some limitations to this study. Major patients mentioned in this paper were hepatic function Child classification A and combination therapy cases were few, so the evaluation about sorafenib using in HCC is not comprehensive. The relative short follow-up visit resulted of lacking evaluation on rare and long-term adverse reactions of sorafenib. Consequently, further studies, such as efficacy in hepatic function Child classification B or C patients, application of sorafenib with concomitant chemotherapy, as well as extended follow-up visit, should be carried out, which will provide clinical practice evidence and are helpful to assess sorafenib comprehensively.

**References**


