Meta-analysis of the Efficacy of Sorafenib for Hepatocellular Carcinoma

Zhao Wang1&, Xiao-Ling Wu1&, Wei-Zheng Zeng1&, Gui-Sen Xu2, Hui Xu1, Min Weng1, Juan-Ni Hou1, Ming-De Jiang1

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 RewMan 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
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).

Table 1. General Characteristic of the Four Eligible Literatures/trials Involved

<table>
<thead>
<tr>
<th>Research</th>
<th>Therapeutic regime</th>
<th>Neutral OS and 95%CI (month)</th>
<th>P value</th>
<th>Neutral TTP and 95%CI (month)</th>
<th>P value</th>
<th>Neutral TTSP and 95%CI (month)</th>
<th>P value</th>
</tr>
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<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>
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<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(2.8-4.2)</td>
<td>0.5</td>
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<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>
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<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></td>
<td>Placebo</td>
<td>6.5(4.5-9.9)</td>
<td>-</td>
<td>5.3(3.8-5.6)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
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</table>

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

Table 2. Overall Survival (OS), Time to Progression (TTP) and Time to Symptomatic Progression (TTSP) Reported in the Four Eligible Literatures/trials

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The search criteria were: 1) Research objects were hepatocellular carcinoma patients; 2) They were clinical randomized controlled trials, not including non-randomized controlled trials and animal and cell experiments; 3) Design of the trials included a) experimental and control groups treated by sorafenib and placebo respectively; b) experimental group treated by sorafenib and another drug products, while control group only received the other drug products. 4) Data should be integrity and the number of cases in experimental and control groups as well as cases finished the trials should be explicit; 5) Clinical index included overall survival (OS), time to progression (TTP), time to symptomatic progression (TTSP), disease control rate (DCR) and adverse reactions.

Literature Evaluation

Literature quality evaluation were conducted following RCT bias risk assessment methods in Cochrane handbook edition 5.0.2, such as the generation of random assortment, allocation concealment implementation, blind method application, data integrity, selective report with or without results, etc.

Data extraction

Data abstraction was conducted by two investigators. With unified form all the research data were extracted and formulated. For each study, we extracted the following information: sample size, cases loss to follow-up and/or withdraw, dosage of sorafenib and research index/data.

Statistical analysis

Meta-analysis was carried out by RevMan 5.0 provided by the Cochrane Collaboration. We examined heterogeneity in results across studies using $\chi^2$ test. We considered a p value of less than 0.05 as indicative of substantial heterogeneity. When substantial heterogeneity was observed, the pooled estimate calculated based on the random-effects model. On the contrary, when substantial heterogeneity was not observed, the pooled estimate calculated based on the fixed-effects model was reported using inverse variance method. Relative risk (RR) was defined as statistic and effect size was presented by 95% confidence interval (CI).

Results

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.
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).

Time to Progression (TTP)

Four papers reported the neutral TTP and its 95%CI (Llovet et al., 2008; Cheng et al., 2009; Abou-Alfa et al., 2010; Kudo et al., 2011). The neutral TTP in sorafenib and control group were 5 months and 2.8 months (P<0.001), 2.8 months and 1.4 months (P=0.005), 6.4 months and 2.8 months (P=0.002), 7.2 months and 5.3 months (P=0.049) respectively, which indicated that sorafenib could prolong TTP of hepatocellular carcinoma patients (Table 2).

Time to symptomatic progression (TTP)

Only two of the four papers reported the neutral TTSP and its 95%CI (Llovet et al., 2008; Cheng et al., 2009), so it’s hard to analysis quantitatively. The neutral TTSP in sorafenib and control group were 4.1 months and 4.9 months (P=0.77), 3.5 months and 3.4 months (P=0.50) respectively, which indicated that sorafenib could NOT prolong TTSP of hepatocellular carcinoma patients (Table 2).

Disease Control Rate (DCR)

Two papers of the four reported the DCR of 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=1.81, 95% CI 1.04 - 2.96; P=0.03) (Figure 2A).

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=3.31, 95% CI 1.54 - 7.11; P=0.006) (Figure 2B).

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 suggested that sorafenib could improve OS of hepatocellular carcinoma patients (RR=1.61, 95% CI 1.20 - 2.15; P<0.001) (Figure 3A).
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**


