RESEARCH ARTICLE

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 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

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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.

Materials and Methods

Search criteria

We reviewed PubMed citations, published in English, concerning sorafenib treating hepatocellular carcinoma from Jan 2000 to July 2012. The keywords included

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

Research	Patients	Cases[&]	Ages[&]	Hepatic function Child classification A (%)[&]	Therapeutic regime[&]	Male/Female ratio[&]	Index
ResearLlovet JM 2008	Europe, America, Oceania	299/303	64.9/66.3	95/98	Sorafenib 400 mg, bid*. Placebo 400 mg, bid.	87:13/87:13	OS, TTP, TTSP, DCR, adverse reaction
Cheng AL 2009	Asian-Pacific region	150/76	51/52	97/97	Sorafenib 400 mg, bid. Placebo 400 mg, bid.	85:15/87:13	OS, TTP, TTSP, DCR, adverse reaction
Abou-Alfa GK 2010	Several nations	47/49	66/65	100/95.9	Doxorubicine 60 mg/m^2, qd**. + Sorafenib 400 mg, bid./Doxorubicine 60 mg/m^2, qd.+ Placebo 400mg, bid	66:34/85.7:1.3	OS, TTP, adverse reaction
Kudo M 2011	Japan, Korea	229/229	69/70	-	Sorafenib 400 mg, bid Placebo 400 mg, bid	76:24/73.4:26.4	OS, TTP, adverse reaction

[&]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

Research	Therapic regime	Neutral OS and 95%CI (month)	*P* value	Neutral TTP and 95%CI (month)	*P* value	Neutral TTSP and 95%CI (month)	*P* value
Llovet JM	Sorafenib	10.7(9.4-13.3)	<0.001	5.5.(4.1-6.9)	<0.001	4.1(-)	0.77
2008	Placebo	7.9(6.8-9.1)		2.8(2.7-3.9)		4.9(-)	
Cheng AL	Sorafenib	6.5(5.6-7.6)	0.014	2.8(2.6-3.6)	0.0005	3.5(2.8-4.24)	0.5
2009	Placebo	4.2(3.7-5.5)		1.4(1.3-1.5)		3.4(2.40-4.08)	
Abou-Alfa GK	Doxorubicine + sorafenib	-	-	6.4(4.8-9.2)	0.02	-	-
2010	Doxorubicine + placebo	-		2.8(1.6-5.0)		-	
Kudo M	Sorafenib	13.7(8.9-NA)	0.006	7.2(5.6-9.1)	0.049	-	-
2011	Placebo	6.5(4.5-9.9)		5.3(3.8-5.6)		-	

sorafenib, hepatocellular carcinoma, liver cancer etc. When more than one publication was identified from the same clinical trial, the most recent or complete report of that trial was used.

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 χ^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.

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).

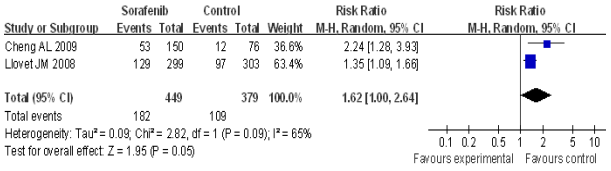

Figure 1. Meta-Analysis Forest Plots of Disease Control Rate in Hepatocellular Carcinoma Patients in Sorafenib And Control Groups

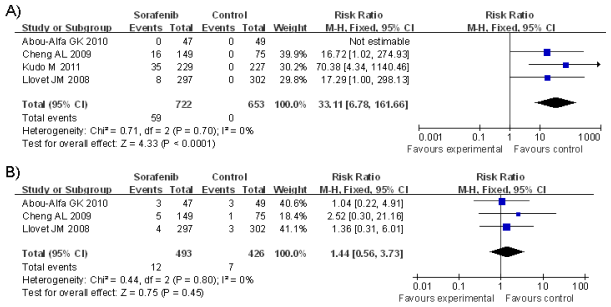

Figure 2. A) Meta-Analysis Forest Plots of Hand-Foot-Skin Reactions Incidence in Hepatocellular Carcinoma Patients in Sorafenib and Control Groups. B) Meta-Analysis Forest Plots of Hypodynamia Occurance Rate in Hepatocellular Carcinoma Patients in Sorafenib and Control Groups

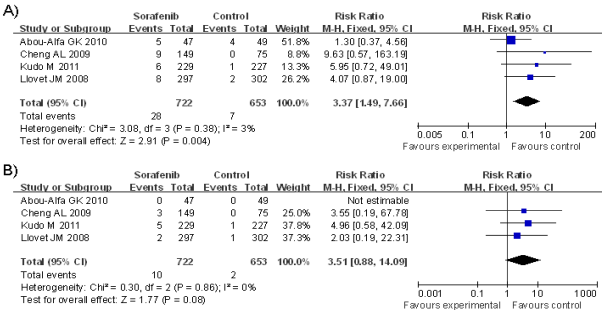

Figure 3. A) Meta-Analysis Forest Plots of Diarrhea Ocurance Rate in Hepatocellular Carcinoma Patients in Sorafenib and Control Groups. B) Meta-Analysis Forest Plots of Hypertension Incidence in Hepatocellular Carcinoma Patients in Sorafenib and Control Groups

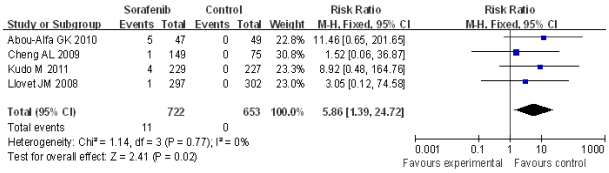

Figure 4. Meta-Analysis Forest Plots of Skin Rash Or Desquamation Incidence In Hepatocellular Carcinoma Patients in Sorafenib and Control Groups

Overall survival (OS)

Three of the four papers only reported the neutral OS and its 95%CI (Llovet et al., 2008; Cheng et al., 2009; Abou-Alfa et al., 2010), so it's hard to analysis quantitatively. The neutral OS in sorafenib and control groups were 10.7 months and 7.9 months (P<0.001), 6.5 months and 4.2 months (P=0.014), 13.7 months and 6.5 months (P=0.006) respectively, which indicated that sorafenib could prolong the survival time of hepatocellular carcinoma patients (Table 2).

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 5.5 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=0.02), 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 (TTSP)

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 4.9months (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=1.62, 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=33.11, 95% CI 6.78 - 161.66; P<0.0001) (Figure 2A).

Hypodynamia

Three papers mentioned hypodynamia occurance. 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 diffrences 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 occurance 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 diffrences 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

Abou-Alfa GK, Johnson P, Knox JJ, et al (2010). Doxorubicin plus sorafenib vs doxorubicin alone in patients with advanced hepatocellular carcinoma. *JAMA*, **304**, 2154-60.

Chen KF, Chen HL, Tai WT, et al (2011). Activation of phosphatidylinositol 3-kinase/Akt signaling pathway mediates acquired resistance to sorafenib in hepatocellular carcinoma cells. *J Pharmcol Exp Ther*, **337**, 155-61.

Cheng AL, Kang YK, Chen Z, et al (2009). Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol*, **10**, 25-34.

Dal Lago L, D'Hondt V, Awada A (2008). Selected combination therapy with sorafenib: a review of clinical data and perspectives in advanced solid tumors. *Oncologist*, **13**, 845-58.

Escudier B, Eisen T, Stadler WM, et al (2007). Sorafenib in advanced clear-cell renal-cell carcinoma. *New Engl J Med*, **356**, 125-34.

Escudier B, Eisen T, Stadler WM, et al (2009). Sorafenib for treatment of renal cell carcinoma: final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. *J Clin Oncol*, **27**, 3312-8.

Furuse J, Ishii H, Nakachi K, et al (2008). Phase I study of sorafenib in Japanese patients with hepatocellular carcinoma. *Cancer Sci*, **99**, 159-65.

Huitzil-Melendez F, Saltz L, Song J, et al (2008). Retrospective analysis of outcome in hepatocellular carcinoma (HCC) patients (pts) with hepatitis C (C+) versus B (B+) treated with sorafenib (S). *In: 2007 Gastrointestinal Cancers Symposium*.

Jemal A, Murray T, Ward E, et al (2005). Cancer statistics, 2005. *CA Cancer J Clin*, **55**, 10-30.

Kudo M, Imanaka K, Chida N, et al (2011). Phase III study of sorafenib after transarterial chemoembolisation in Japanese and Korean patients with unresectable hepatocellular carcinoma. *Eur J Cancer*, **47**, 2117-27.

Liu L, Cao Y, Chen C, et al (2006). Sorafenib blocks the RAF/MEK/ERK pathway, inhibits tumor angiogenesis, and induces tumor cell apoptosis in hepatocellular carcinoma model PLC/PRF/5. *Cancer Res*, **66**, 11851-8.

Llovet JM, Ricci S, Mazzaferro V, et al (2008). Sorafenib in advanced hepatocellular carcinoma. *New Engl J Med*, **359**, 378-90.

Parkin DM, Pisani P, Ferlay J (2008). Global cancer statistics. *CA Cancer J Clin*, **49**, 33-64.

Villanueva A, Newell P, Chiang DY, et al (2007). Genomics and signaling pathways in hepatocellular carcinoma. *Semin Liver Dis*, **27**, 55-76.

Wilhelm S, Carter C, Lynch M, et al (2006). Discovery and development of sorafenib: a multikinase inhibitor for treating cancer. *Nat Rev Drug Discov*, **5**, 835-44.