Int J Clin Exp Pathol 2019;12(7):2389-2397
www.ijcep.com /ISSN:1936-2625/IJCEP0094030

Review Article

Antineoplastic effects of sorafenib on primary liver cancer: a systematic review and meta-analysis

Meizhen Liu[1*], Rui Zhou[2*], Xiaoliu Liang[1], Min Su[3], Rong Li[3], Bin Yang[1]

[1]College of Pharmacy, Guangxi Medical University, Nanning 530021, Guangxi, PR China; [2]Department of Hepatobiliary Surgery, Guigang City People's Hospital, The Eighth Affiliated Hospital of Guangxi Medical University, Guigang, Guangxi, PR China; [3]Key Laboratory of Tumor Immunology and Microenvironmental Regulation, Guilin Medical University, Guilin, Guangxi, PR China. [*]Equal contributors.

Received March 18, 2019; Accepted April 23, 2019; Epub July 1, 2019; Published July 15, 2019

Abstract: Objective: The current study aimed to investigate the therapeutic efficacy of sorafenib against primary liver cancer (PLC). Methods: Four databases (PubMed, CNKI, WanFang and Civip) were used to search and assess all clinical randomized controlled trials regarding the clinical efficacy of sorafenib-exerted anti-PLC from November 20, 2006 to May 8, 2018. Results: A total of 15 randomized controlled trials were included in this analysis, and 1102 patients with PLC were randomly assigned as sorafenib group (521 cases), and control group (581 cases). Compared to controls, the sorafenib group showed significant clinical efficacy (overall: OR, 3.38; 95% CI, 2.57-4.46; $P < 0.05$), which was notably effective in all subgroups with different treatment durations (all $P < 0.05$). In addition, further analysis in subgroups exhibited that the clinical efficacy of treatment duration greater than 100 days was higher than that of control groups (OR, 4.61; 95% CI, 2.58-8.29; $P < 0.05$). Conclusion: Sorafenib has clinical efficacy for treating PLC, and the treatment duration in PLC patients shows limited impact on the therapeutic efficacy of sorafenib. Furthermore, sorafenib can extend the survival rate in patients with PLC.

Keywords: Sorafenib, therapeutic efficacy, survival rate, meta-analysis

Introduction

Primary liver cancer (PLC) is a malignant tumor that occurs in hepatocytes or intrahepatic bile duct epithelial cells, and PLC is one of the leading causes of cancer death in China [1, 2]. Globally, around 250,000 people die of PLC every year, and China accounts for 45% of them approximately [3]. PLC is diagnosed mostly in a middle-aged population, in which the ratio of male to female prevalence is 5:1 [4]. In addition, epidemiologic data show that PLC ranks third in the world as a cancer killer, and the prevalence of PLC in China ranks first nationwide [5, 6]. PLC seriously threatens human health and quality of life, thus, to conduct research on PLC prevention and treatment is very important. In clinical practice, surgical resection can achieve a satisfactory outcome, but the majority of patients with PLC are diagnosed at advanced stage before the option for resection [7-10]. Sorafenib is an oral multikinase inhibitor that is a targeted therapy for the treatment of PLC. It suppresses tumor growth directly through affecting tyrosine protein kinases, such as VEGFR, PDGFR, and Raf [11, 12]. In addition, sorafenib mediates blockage of intratumoral neovascularization to directly inhibit the growth of tumor cells [13-15]. Although sorafenib has been prescribed in the clinical treatment for PLC, the wide use of sorafenib in China is limited because of the expensive price. Furthermore, limited reviews regarding the therapeutic efficacy of sorafenib are reported in China [8]. Therefore, our current review was designed to systematically evaluate the clinical efficacy of sorafenib in the treatment of PLC through searching for data of clinical trials in sorafenib treatment of PLC and further reviewing this systematic meta-analysis.

Methods and materials

Study identification and search strategy

We conducted this review on the basis of the criteria published in the Preferred Reporting Items for Systematic Reviews and meta-analy-

Figure 1. Bias assessment of 15 included RCTs.

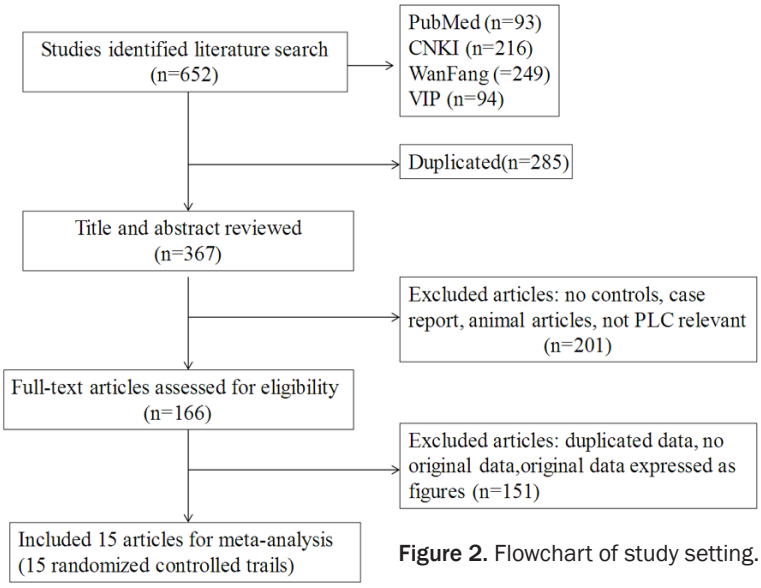

Figure 2. Flowchart of study setting.

ses (PRISMA) guidelines. The studies were supported by the local Ethnic Committee and followed by the statement of Declaration of Helsinki. We identified the relevant evidences of the therapeutic effect of sorafenib in PLC patients through systematically searching CNKI, PubMed, Chinese-Cqvip and WanFang databases. The search strategy was used as: ("sorafenib" or "Nexavar" or "Sorafenib tosylate") and ("primary liver cancer" or "PLC" or "primary hepatic carcinoma" or "HCC"). In addition, we performed an extensive search, and the literature was further verified in reference lists.

Inclusion and exclusion criteria

Inclusion criteria for studies were as follows: (1) the study should report the therapeutic effectiveness of sorafenib against PLC patients; (2) randomized controlled trials (RCT); (3) no duplicated data in study; (4) report the total number of cases in sorafenib group and control group, and use the complete remission (CR), partial remission (PR), stable (SD), progression (PD) as the efficacy indicators, and objectively effective (OR) = CR + PR; (5) PLC patients with pregnancy included; (6) patients with any treated duration considered; (7) the diagnosis clearly defined as PLC (according to national diagnostic criteria); (8) the sorafenib group and the control group simultaneously used conventional, symptomatic, and supportive treatment. The control group as a blank control, placebo control or other drugs (including Chinese and Western medicine).

Table 1. Characteristics of therapeutic effect of sorafenib against PLC

Author	Year	Country	Duration	Obvervational index	Treatment group					Control group				
					SZ	M/F	Age (years)	Events	Intervention trial	SZ	M/F	Age	Events	Intervention control
Huijie Zhang	2015	China	28 days	VEGF, bFGF	16	11/5	< 50 = 10# ≥ 50 = 6#	8	Sorafenib, TACE	32	26/6	< 50 = 25# ≥ 50 = 7#	7	TACE
Lili Ma	2015	China	45 days	mRECIST, AFP	23	19/4	60.45±9.67	6	Sorafenib, TACE	34	31/3	57.63±10.38	6	TACE
Dan Jin	2017	China	6 months	mRECIST	37	22/15	46.7±13.3	27	Sorafenib, TACE	51	30/21	40.7±15.3	18	TACE
Fei Chen	2016	China	6 months	mRECIST	44	NR	NR	37	Sorafenib, TACE	32	NR	NR	20	TACE
Xiaobing Li	2014	China	8 weeks	Tumor size	30	18/12	51.3±5.5	26	Sorafenib, SRT	30	16/14	50.9±5.2	18	SRT
Mingqin Wei	2014	China	1 month	Tumor size	15	9/6	39.7±6.8	11	Sorafenib, Microwae ablation, Vascular intervention	34	21/13	41.2±7.1	12	Microwave ablation, Vascular intervention
Haixiao Zhang	2015	China	1 month	Tumor size	52	28/24	≤ 60 = 27# > 60 = 25#	48	Sorafenib, RFA	68	31/37	≤ 60 = 36# > 60 = 32#	51	RFA
Nansong Yu	2018	China	3 months	Tumor size, AST, ALT, TBiL	23	17/6	58.19±4.34	21	Sorafenib, Radiofrequency ablation	23	16/7	58.25±4.31	15	Radiofrequency ablation
Siming Chen	2012	China	3 months	RECIST, AFP	28	20/8	NR	16	Sorafenib, TACE	28	17/11	NR	7	TACE
Rengui Zhou	2014	China	NR	Tumor size	48	34/14	71.9±12.7	25	Sorafenib, TACE	48	31/17	67.9±10.8	16	TACE
Yong Tan	2015	China	3 months	mRECIST, AFP	29	19/10	52.3±5.1	12	Sorafenib, TACE	28	17/11	53.1±5.3	4	TACE
Wei Liu	2017	China	12 weeks	Tumor size	28	NR	67.7±1.5	24	Sorafenib, TACE	28	NR	67.1±1.4	19	TACE
Jiahang Xie	2015	China	13 weeks	Tumor size, AFP	43	34/9	54.2±7.1	33	Sorafenib, TACE	40	30/10	53.9±7.5	22	TACE
Changshan Huang	2017	China	12 weeks	VEGF, bFGF/RECTST	60	43/17	65.17±8.41	30	Sorafenib, TACE	60	44/16	65.22±8.37	13	TACE
Xiao Sun	2018	China	1 month	VEGF, bFGF, RECTST	45	31/14	48.5±7.2	33	Sorafenib, Microwave ablation	45	30/15	47.6±7.1	21	Microwave ablation

NR, no repotr; SZ, sample size; M/F, male/female; #, Number of people in a certain age range.

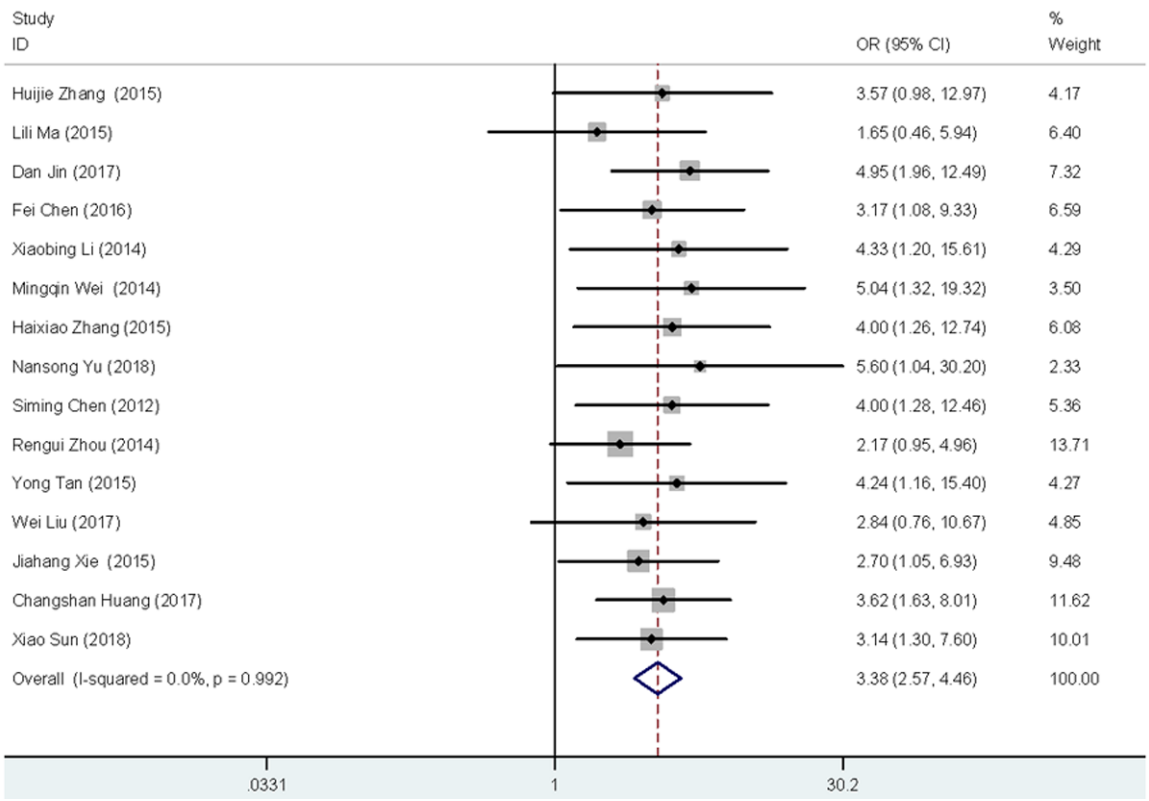

Figure 3. Forest plots for the therapeutic effect of sorafenib in the treatment of PLC with fixed effect model (OR, 3.38; 95% CI, 2.57-4.44; P > 0.05).

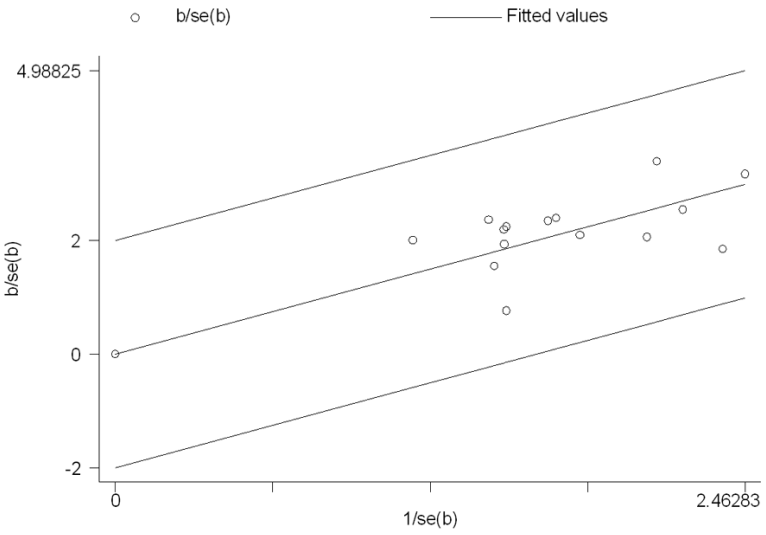

Figure 4. Galbraith diagram.

Exclusion criteria were: (1) duplication: same studies came from different database; (2) animal studies, reviews, case reports, and personal experience summaries; (3) no controls or not PLC relevant; (4) no original data or original data expressed as figures; (5) studies not meeting the inclusion criteria of this study.

Quality assessment and data extraction

A literature search, data extraction and study selection were conducted independently by two reviewers (Xiaoliu Liang and Meizhen Liu). The quality of each RCT was independently evaluated according to Cochrane's systematic review of quality evaluation criteria. The quality evaluation included: (1) whether the random method was correct, and analyzed the similarity of the baseline between the groups to assist in the evaluation of selective bias; (2) whether the allocation scheme was hidden; (3) whether the double-blind method was adopted; (4) whether the result processing adopted intentional processing (Intention to treat, ITT); (5) reports of withdrawal or loss of

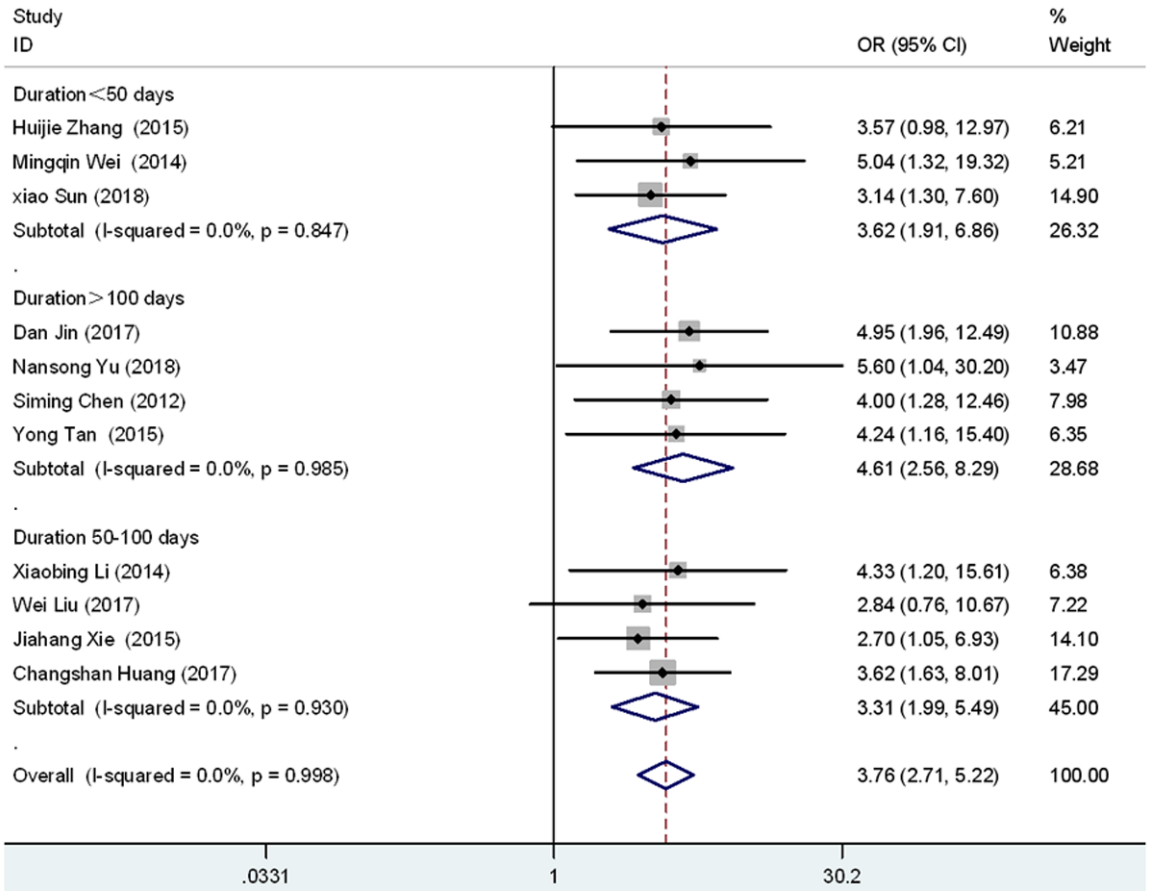

Figure 5. Forest plots for the therapeutic effect of sorafenib in the treatment of PLC in treated durations subgroup analysis with fixed effect model (< 50 days: OR, 3.62; 95% CI, 1.91-6.86; P < 0.05; > 100 days: OR, 4.61; 95% CI, 2.56-8.29; P < 0.05; 50-100 days: OR, 3.31; 95% CI, 1.99-5.49; P < 0.05; overall: OR, 3.76; 95% CI, 2.71-5.22; P < 0.05).

follow-up. For each RCT study, a risk assessment of bias was performed according to the following criteria: "low risk of bias" indicates that the risk of bias in the study is low; "unclear risk of bias" indicates the possibility of risk of bias because the study does not provide sufficient information; "high risk of bias" indicates a higher likelihood of a risk of bias in the study (**Figure 1**). The information extracted was: (1) name of the first authors; (2) year of publications; (3) country of studies; (4) treated durations; (5) sample size of the patients of PLC; and (6) the events of sorafenib group and control group. Disagreements were handled with a third investigator (Min Su) through discussion.

Statistical analysis

Stata 12.0 software was used in this meta-analysis. The data was showed as Tevents, Ttotal, Cevents and Ctotal, and clarified the therapeutic effect of sorafenib in against PLC patients in sorafenib group vs. controls, and the statistical heterogeneity was estimated by Chi-squared Q test and I^2 statistics. When P < 0.05 or I^2 > 50%, we used a random-effect model; otherwise a fixed-effect model. In this study, when P > 0.05 and I^2 < 50%, we use a fixed-effect model. Considering the effect of treatment durations, patients were divided into three groups (group 1: < 50 days; group 2: 50-100 days; group 3: > 100 days) for subgroup analysis. We conducted sensitivity analysis by selecting literatures with high scores. An Egger's test was performed to examine the publication bias and a P < 0.05 was representative of significant publication bias.

Results

Selection and characteristics of study

The flowchart of this review and meta-analysis is shown (**Figure 2**). Initially, we identified 652

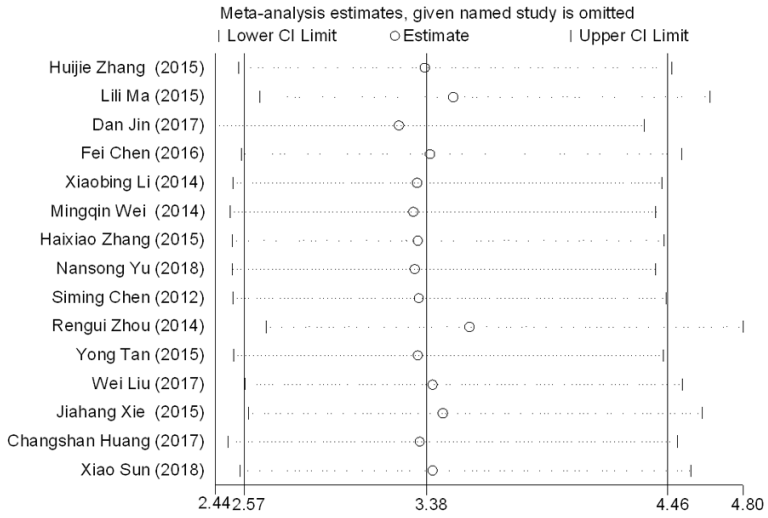

Figure 6. Sensitivity analysis.

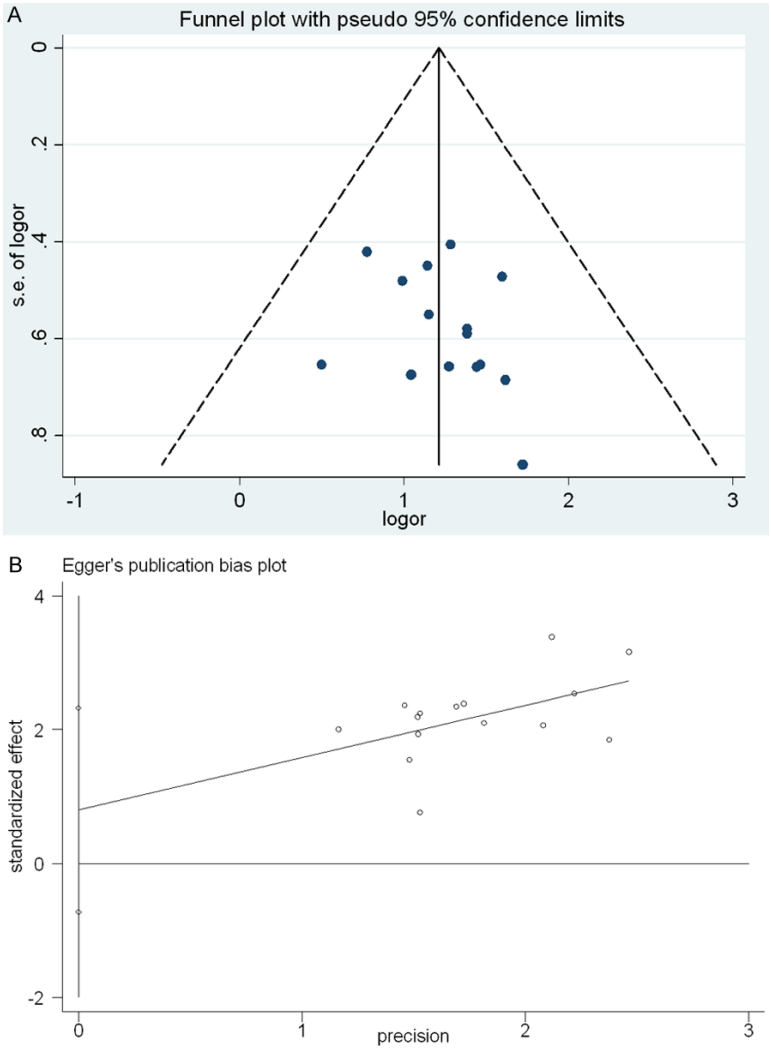

Figure 7. Publication bias regarding the therapeutic effect of sorafenib in the treatment of PLC (A: Funnel plot; B: Publication bias, t = 1.13; P = 0.278; 95% CI, -0.72 to 2.32).

potential studies and 285 publications were excluded for duplication. Furthermore, 201 papers were excluded for no controls linking with PLC relevance, review articles or animal studies. Additionally, we excluded 151 articles without related original data. Further, 15 papers [7, 16-29] were followed by the requirement of this meta-analysis involving 15 randomized controlled trials of sorafenib group (521 cases) and control group (581 cases). Specific characteristics in 15 papers are shown (**Table 1**).

Results of meta-analysis and subgroup analysis

Compared to the controls, the sorafenib group resulted in significant therapeutic efficacy on PLC treatment (OR, 3.36; 95% CI, 2.55-4.44; P = 0.000 < 0.05) (**Figure 3**). This result of meta-analysis showed that there was no heterogeneity (OR, 3.36; 95% CI, 2.55-4.44; P = 0.992 > 0.05; I^2 = 0% < 50%). In addition, the Galbraith diagram suggested that there was no heterogeneity in this meta-analysis (**Figure 4**). Subgroup analysis was conducted to explore the effectiveness of duration on sorafenib in the treatment of PLC. As shown in **Figure 5**, compared to thecontrol group, the therapeutic efficacy of sorafenib in PLC was notably greater than that in the subgroup with different treatment duration (all P < 0.05).

Sensitivity analysis

Further, sensitivity analysis was done to evaluate the reliability of these outcomes in meta-analysis through selecting literatures with high sco-

Table 2. Survival rate of sorafenib in treatment of PLC

Author	Year	Survival situation
Huijie Zhang	2015	NR
Lili Ma	2015	The median survival time was 14.9 months in treatment group, significantly higher than 8.7 months in the control group ($P < 0.05$).
Dan Jin	2017	NR
Fei Chen	2016	The 1a and 2a survival rates of the treatment group were 68.2% and 43.2%, respectively, while those in the control group were 50.0% and 31.3%, respectively, and the difference between the two groups was significant ($P < 0.05$).
Xiaobing Li	2014	The 1-year and 2-year survival rates of the treatment group were higher than those of the control group, and the differences were statistically significant ($P < 0.05$).
Mingqin Wei	2014	NR
Haixiao Zhang	2015	There were no significant differences in 1- and 2-year survival rates between the treatment group (94.2%, 80.7%) and the control group (79.4%, 63.2%) ($P > 0.05$), and there was a significant difference in 3-year survival rate between the treatment group (71.1%) and the control group (39.7%) ($P < 0.05$). The median survival time was longer in treatment group (23.1 months) than in control group (16.7 months) ($P < 0.05$).
Nansong Yu	2018	The treatment group after treatment for 1 years and 2 years survival rates were 86.96%, 78.26%, the control group after treatment for 1 years and 2 years survival rates were 60.87% and 47.83%. The treatment group was significantly higher than the control group ($P < 0.05$).
Siming Chen	2012	Treatment group half year survival rate, 1-year survival rate, and 2-year survival rates were 100%, 80.9%, 75.0% respectively, higher than that in the control group of 78.6%, 60.7%, 42.9%, and there was significant difference ($P < 0.05$).
Rengui Zhou	2014	The survival rates of one year and more than two years were 89.6% and 72.9% in the treatment group were higher than those of the patients in the control group (58.3% and 35.4%) with significant differences ($P < 0.05$).
Yong Tan	2015	The middle level of PFS in the treatment group was 10 months, significantly higher than that in the control group (6 months) ($P < 0.05$).
Wei Liu	2017	NR
Jiahang Xie	2015	The 1, 2, 3 year survival rate were 74.4%, 44.2% and 14.0% in treatment group and 52.5%, 32.5% and 10.0% in the control group, respectively. The difference of 1 year survival rate between the two groups was significantly different ($P < 0.05$) while no significant difference was observed in 2 and 3 year survival rate between these two groups ($P > 0.05$).
Changshan Huang	2017	NR
Xiao Sun	2018	The median survival time, median survival, and 1 year survival rate were significantly higher in the treatment group than in the control group, and the recurrence rate was significantly lower than that of the control group ($P < 0.05$).

NR, no report.

res. As result, all outcomes stayed consistent (**Figure 6**).

Publication bias

In addition, funnel plot (**Figure 7A**) and Egger's test ($t = 1.13$; $P = 0.278$; 95% CI, -0.72 to 2.32) (**Figure 7B**) exhibited no significant publication bias in this meta-analysis.

Discussion

PLC is the most common type of hepatic cancer in adults. The majority of PLC cases occur in Asia, especially in China [30]. In addition to surgical resection, chemotherapy is resultant clinical strategy for PLC treatment. Sorafenib is a kinase inhibitor drug approved for the therapy of advanced PLC [31]. Sorafenib therapy triggers cell apoptosis, which may halt tumor growth [10, 32]. In addition, sorafenib may induce autophagy in cancer cells, but autophagy can also result in drug tolerance [33]. Thus, clinical effectiveness of sorafenib must be assessed by a group of literature assays. The main focus of this study was the short-term efficacy of sorafenib treatment, namely OR. The results showed the OR of clinical efficacy in sorafenib group was better than that in the control group, an outcome that was basically consistent with the previous reports, suggesting that sorafenib combined with conventional therapy for the treatment of PLC is more effective than conventional monotherapy. In addition, combination therapy could synergize and enhanced the efficacy. Among the 15 papers included in the meta-analysis, 10 of them mentioned the outcomes of the survival rate. Furthermore, the results revealed that sorafenib-treated PLC could achieve a higher effectiveness rate, longer survival time, and more stable disease status through induction integration (**Table 2**). These comparable data were basically consistent with the findings of Strebel et al. [34].

In this systematic review and meta-analysis, results showed that the therapeutic efficacy of the sorafenib group was better than that of the controls, but some of the randomized methods

included in the study were unclear, such as no allocation concealment and blindness used, limited number of samples, and no sample number estimated in all studies. Therefore, the therapeutic effectiveness of sorafenib may be exaggerated. Collectively, in order to propose a convincing conclusion in this topic, further multi-center randomized and double-blind controlled trials are still needed.

Conclusions

Taken together, this meta-analysis reveals that the clinical effectiveness of sorafenib against PLC is initially confirmed. However, whether the therapeutic efficacy of sorafenib in PLC is better than conventional monotherapy or symptomatic treatments is uncertain, and a rigorous, large-sample randomized double-blind controlled trial is needed.

Acknowledgements

This report was funded in part by National Natural Science Foundation of China (No. 81660610, 81660091, 81560134), and National Natural Science Foundation of Guangxi (No. 2016GXNSFBB39006, 2016GXNSFBA380055).

Disclosure of conflict of interest

None.

Address correspondence to: Rong Li, Key Laboratory of Tumor Immunology and Microenvironmental Regulation, Guilin Medical University, Huan Cheng North 2nd Road 109, Guilin, Guangxi, PR China. Tel: +86-773-5895882; E-mail: lirong1278@163.com; Bin Yang, College of Pharmacy, Guangxi Medical University, No. 22 Shuangyong Road, Nanning 530021, Guangxi, PR China. Tel: +86-771-8216-9114; E-mail: gxmu_yangbin@126.com

References

[1] Dai ZL, Zhao Y. Comprehensive treatment for primary liver cancer. Chinese Journal of Bases and Clinics In General Surgery 2014; 21: 133-137.

[2] Peng PC, Chen R, Wen B, Deng X. Efficacy and safety of sorafenib in the treatment of advanced primary hepatic carcinoma: a systematic review. Chinese General Practice 2014; 17: 3368-3374.

[3] Guo NJ. Sensitizative effect of sorafenib on hepatocellular carcinoma cell line HepG2 [M]: Southern Medical University; 2008.

[4] Yang WT, Hou EC. The research progress of primary hepatic carcinoma treatment. Journal of Modern Oncology 2016; 24: 3495-3499.

[5] Zhang JK, Wang YY. Advances in research on the mechanism and treatment of primary liver cancer. China Pharmacy 2015; 26: 4171-4173.

[6] Qin LY, Wang B, Ni ZH, et al. Mechanism and significance of sorafenib-induced autophagy in HepG2 cells. Acta Academiae Medicinae Militaris Tertiae 2013; 35: 2435-2438.

[7] Zhang HJ, Guo WD, Qu ZJ. The efficacy and serum VEGF, bFGF changes of TACE combined with Sorafenib in the treatment primary liver cancer. Journal of Modern Oncology 2015; 23: 3164-3168.

[8] Yang LQ, Qin SD, Gong XL, et al. Clinical study of sorafenib in the treatment of advanced primary liver cancer in Chinese. Chinese Journal of New Drugs 2013; 22: 2053-2059.

[9] Cui Y. Study on the inhibitory effect of sorafenib combined with heparin/dalofurin on tumor [M]: Southern Medical University; 2008.

[10] Guo XL, Li J. Clinical study on compound Kushen injection combined with sorafenib in treatment of advanced primary hepatocellular carcinoma. Modern Medicine And Clinical 2017; 32: 258-262.

[11] Gong XL, Qin SD. Research progress on treatment of sorafenib for Chinese patients with advanced hepatocellular carcinoma. Chinese Clinical Oncology 2015; 20: 175-184.

[12] Qin SD, Gong XL. Progress in the treatment of primary liver cancer with sorafenib. Chinese Clinical Oncology 2008; 13: 1057-1068.

[13] Cui YJ, Zheng H. Research progress of sorafenib for the treatment of hepatocellular carcinoma. The Chinese Journal of Clinical Pharmacology 2014; 30: 739-741.

[14] Du HL, Yang WP, Chen L, et al. Effect and mechanism of sorafenib in inhibiting autophagy of HepG2 cells proliferation. Journal of Surgery Concepts and Practice 2011; 16: 270-274.

[15] Zhou AP, Sun Y. Recent advances in sorafenib: a multiple targeted anti-tumor agent. Oncology Progress 2006; 6: 529-533.

[16] Ma LL, Han ZC, Liu J. Efficacy and safety of transarterial chemoembolization combined with sorafenib in patients with hepatocellular carcinoma. The Chinese Journal of Clinical Pharmacology 2015; 31: 1497-1499.

[17] Jin D, Zhou L, Wu MY, et al. Therapeutic effect of transcatheter arterial chemoembolization combined with sorafenib in the treatment of primary liver cancer. Chinese Medicine of Factory and Mine 2017; 30: 339-341.

[18] Chen F, He LL, Wang S, Bao RL. Combination of sorafenib and transcatheter arterial chemoembolization in treatment of patients with primary liver cancer. Journal of Clinical Hepatology 2016; 19: 356-357.

[19] Li XB, Yan WH. Short-term efficacy of stereotactic radiotherapy combined with sorafenib in the treatment of recurrent hepatocellular carcinoma. Modern Medicine Health 2014; 30: 2456-2458.
[20] Wei MQ, Xu XM. Research on thermal therapy, intervention combined with sorafenib in treatment of primary liver cancer. Modern Journal of Integrated Chinese Traditional and Western Medicine 2014; 23: 4006-4009.
[21] Zhang HX, Guan QL, Ren WX, Gu JP. Radiofrequency ablation plus sorafenib for hepatocellular carcinoma. Journal of Practical Diagnosis and Therapy 2015; 29: 409-411.
[22] Nan S, Yan PJ, Zheng YY, Lu BC. Effect of radiofrequency ablation combined with sorafenib on liver function in patients with advanced hepatic carcinoma. Applied Journal of General Practice 2018; 16: 754-756.
[23] Chen SM, Wang YS, Xie H. Clinical observation of sorafenib combined with transcatheter arterial chemoembolization for treating senile primary carcinoma of the liver. China Journal of Modern Medicine 2012; 22: 71-73.
[24] Zhou RG, Zhou XJ, Li XY, Xia YB, Song P, Guo XD. Clinical effects of sorafenib combined with transcatheter arterial chemoembolization on the treatment of advanced primary hepatocellular carcinoma. Progress in Modern Biomedicine 2014; 14: 2494-2496.
[25] Tan Y, Zhang T, Peng JJ, Zhao Y. Curative effect of sorafenib combined with transcatheter arterial chemoembolization in treatment of large primary liver cancer. Medical Journal of National Defending forces in Southwest China 2015; 25: 386-9.
[26] Liu W. Therapeutic effect of sorafenib on advanced primary liver cancer. Strait Pharmaceutical Journal 2017; 29: 184-185.
[27] Xie JH, Wang JH. Analysis of efficacy and complications of sorafenib combined with transcatheter arterial chemoembolization (TACE) for advanced hepatocellular carcinoma. Sichuan Journal of Cancer Control 2015; 28: 152-154.
[28] Huang CS, Yu W, Wang Q, Ding YC, Ma C, Huang T. Clinical efficacy of sorafenib and TACE for primary liver cancer and its effect on bFGF and VEGF level. The Practical Journal of Cancer 2017; 32: 943-945.
[29] Sun X, Xu EX, Qiu CY, Dong Y. Effect of microwave ablation combined with sorafenib in the treatment of primary liver cancer. The Practical Journal of Cancer 2018; 33: 664-667.
[30] Gong XL, Qin SD. New progress in molecular targeted therapy for primary liver cancer. Chinese Clinical Oncology 2008; 1-10.
[31] Ding L, Cheng G. Multi-targeted antineoplastic agent sorafenib: advanced in pharmacologic and clinical research. Adverse Drug Reactions Journal 2007; 153-157.
[32] Chen J. Relationship between ERK phosphorylation level and sensitivity of sorafenib in hepatocellular carcinoma [M]: Zhejiang University; 2016.
[33] Guo XC. Clinicopathological characteristics, survival prognosis and hypoxia-induced resistance mechanism of sorafenib tosylate in patients with advanced primary hepatocellular carcinoma [M]: Chinese People's Liberation Army Medical College; 2016.
[34] Strebel BM, Dufour JF. Combined approach to hepatocellular carcinoma: a new treatment concept for nonresectable disease. Expert Rev Anticancer Ther 2008; 8: 1743-9.