RESEARCH ARTICLE

Efficacy and Safety of Sorafenib for Advanced Non-Small Cell Lung Cancer: a Meta-analysis of Randomized Controlled Trials

Wei-Lan Wang[1&], Zhi-Hui Tang[1&], Ting-Ting Xie[1&], Bing-Kun Xiao[2&], Xin-Yu Zhang[4], Dai-Hong Guo[1], Dong-Xiao Wang[1], Fei Pei[1], Hai-Yan Si[3], Man Zhu*

Abstract

Background: Many clinical trials have been conducted to evaluate sorafenib for the treatment of advanced NSCLC, but the results for efficacy have been inconsistent. The aim of this study was to evaluate the efficacy and safety of sorafenib in patients with advanced NSCLC in more detail by meta-analysis. Methods: This meta-analysis of randomized controlled trials (RCTs) was performed after searching PubMed, EMBASE, ASCO Abstracts, ESMO Abstracts, and the proceedings of major conferences for relevant clinical trials. Two reviewers independently assessed the quality of the trials. Outcomes analysis were disease control rate (DCR), progression- free survival (PFS), overall survival (OS) with 95% confidence intervals (CI) and major toxicity. Subgroup analysis was conducted according to sorafenib monotherapy, in combination with chemotherapy or EGFR-TKI to investigate the preferred therapy strategy. Results: Results reported from 6 RCTs involving 2, 748 patients were included in the analysis. Compared to sorafenib-free group, SBT was not associated with higher DCR (RR 1.31 (0.96- 1.79), *p*=0.09), PFS (HR 0.82 (0.66-1.02), *p*=0.07) and OS (HR 1.01 (0.92-1.12), *p*=0.77). In terms of subgroup results, sorafenib monotherapy was associated with significant superior DCR and longer PFS, but failed to show advantage with regard to OS. Grade 3 or greater sorafenib-related adverse events included fatigue, hypertension, diarrhea, oral mucositis, rash and HFSR. Conclusions: SBT was revealed to yield no improvement in DCR, PFS and OS. However, sorafenib as monotherapy showed some activity in NSCLC. Further evaluation may be considered in subsets of patients who may benefit from this treatment. Sorafenib combined inhibition therapy should be limited unless the choice of platinum-doublet regimen, administration sequence or identification of predictive biomarkers are considered to receive better anti-tumor activity and prevention of resistance mechanisms.

Keywords: Sorafenib - non-small cell lung cancer - meta-analysis - RCTs

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Introduction

Lung cancer is the leading cause of cancer-related deaths for both man and women worldwide, with a low 5-year survival rate (approximately 15%) (Jemal et al., 2010). In 2008, an estimated 520, 000 patients were newly diagnosed with lung cancer in China; 222, 500, in the United States; 11, 000, in the Netherlands; and over 1.2 million globally (Ferlay et al., 2010). Platinum-based chemotherapy doublets are the backbone of therapy for patients with advanced NSCLC (Schiller et al., 2002). The median overall survival ranges from 7 to 12 months with first-line chemotherapy (Sandler et al., 2006; de Marinis et al., 2008). Prolongation of survival and improving quality of life are the major therapeutic goals for patients with metastatic disease. Over the past ten years, a number of medications have been approved for NSCLC, but new treatment options are urgently needed.

Sorafenib is a small-molecule multi-targeted kinase inhibitor that blocks the activation of C-RAF, B-RAF, c-KIT, FLT-3, RET, vascular endothelial growth factor receptor 2 (VEGFR-2), VEGFR-3 and platelet-derived growth factor receptor (Wilhelm et al., 2004). It has been approved for advanced renal cell carcinoma and hepatocellular carcinoma (Escudier et al., 2007; Llovet et al., 2008). Many clinical trials have been conducted to evaluate sorafenib in the treatment of advanced NSCLC, either as a single agent, in combination with chemotherapy or targeted agents, but the results on the efficacy of such trials are inconsistent (Scagliotti et al., 2010; Molina et al., 2011; Spigel et al., 2011; Paz-Ares L et al., 2012; Paz-Ares et al., 2012; Wakelee et al., 2012). Therefore, we have undertaken this meta-analysis to evaluate the available evidence from the relevant RCTs. And subgroup analysis was conducted according to sorafenib monotherapy, in combination with chemotherapy or targeted agents to

[1]Department of Pharmaceutical Care, [3]Department of Oncology, Chinese PLA General Hospital, [2]Department of pharmacochemistry, Institute of Radiation Medicine, Beijing, [4]Department of Pharmacy, Bengbu Medical University, Bengbu, China [&]Equal contributors
**For correspondence: wwl100@sohu.com*

investigate the preferred therapy strategy.

Materials and Methods

Search Strategy

We have collected the eligible trials by searching the PubMed EMBASE, ASCO Abstracts, ESMO Abstracts for relevant clinical trials up to December 2013. Moreover, we also searched in http://www. Clinical Trials.gov websites for information on registered randomized controlled trials. The keywords were used as follow: "NSCLC, " "non-small-cell lung cancer, " OR "lung neoplasm, " OR "lung cancer, " AND "multitargeted antiangiogenesis tyrosine kinase inhibitors, " OR "sorafenib".All the randomized controlled trials on sorafenib for NSCLC were collected and identified. In addition to computer browsing, review articles and original papers were scanned in the reference section to look for trials that may have been overlooked. Papers published in English or Chinese were included.

Inclusion Criteria

The randomized controlled trials (RCTs) were eligible for inclusion in our meta-analysis if sorafenib-based therapy (SBT) was compared with control arms in first-line, second-line treatment or multi-line treatment of advanced NSCLC. All patients with previously treated or untreated locally advanced (stage IIIB) or metastatic (stage IV) NSCLC; phase II and III RCTs were included. Trials were excluded if they did not meet the above inclusion criteria.

Data Extraction and Quality Assessment

Data abstraction and quality assessment were conducted independently by two reviewers. Disagreements were resolved by discussion with an independent expert. The following information was extracted from each paper: trial's name, first author, year of publication, number of patients in two groups, sex, age, performance status (smoking history, histology and PS). Types of outcome measures included overall survival (OS), progression-free survival (PFS), disease control rate (DCR) and toxicities. Only grade 3 or greater adverse events were analyzed.

We assessed methodological quality of the studies using the Jadad score (Jadad et al., 1996). We graded each parameter of trial quality as full score (5), high score (≥3), and low score (≤2).

Statistical Analysis

Time-to-event outcomes were compared using a hazard ratio (HR). Dichotomous data were compared using a risk ratio (RR). Statistical heterogeneity in the results of the trials was assessed by the chi-square test, and expressed by the I^2 index (Higgins et al., 2003). When there was no statistically significant heterogeneity, a pooled effect was calculated with a fixed-effect model. When considerable heterogeneity was found (p<0.1, or I^2>50%), a random effect model was employed. Subgroup analyses were performed to determine if the results were influenced by different SBT (sorafenib monotherapy, in combination with chemotherapy or EGFR-TKI). All p values were two-sided. All CI had two-sided probability coverage of 95%.

All meta-analysis were performed using Review Manager 5.2.

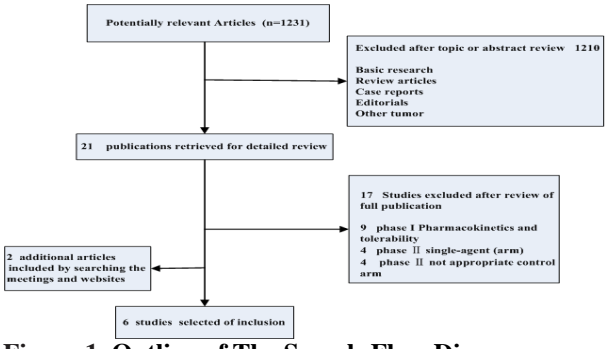

Figure 1. Outline of The Search-Flow Diagram

Results

Characteristics of the included trials

A total of 1231 potentially relevant articles were reviewed. After exclusion of duplicate and irrelevant studies, our search yielded six eligible trials involving 2748 patients that were retrieved for evaluation that is more detailed. There were 1409 and 1339 patients randomized to SBT and to the control arms, respectively. Of the included studies, two studies compared sorafenib alone vs. placebo (Paz-Ares L et al., 2012; Wakelee et al., 2012), one study compared sorafenib plus EGFR-TKIS vs. EGFR-TKIS (Spigel et al., 2011), three studies compared sorafenib plus chemotherapy vs. chemotherapy (Scagliotti et al., 2010; Molina et al., 2011; Paz- Ares LG, et al., 2012). The process of study selection is shown in a flow chart (Figure 1). Characteristics of the included trials were provided in Table 1.

Jadad score was used to assess the quality of the included trials. Overall, two trials scored 5, three scored 4, one scored 3.

Disease control rate (DCR)

Just 5 trials on the data of DCR were available, including 2648 patients. The trial by Molina et al. didn't give the data of DCR (Molina et al., 2011). Heterogeneity was found in analysis of DCR (I^2=95.1%), so the random-effect model was used. The meta- analysis failed to show any significant benefit of SBT vs. sorafenib-free group in the DCR (RR 1.31 (0.96-1.79), p=0.09). Further, subgroup analyses were performed according to different SBT.

In the subgroup analysis, the result was consistent, no significantly statistical difference in DCR was detected between combination with chemotherapy (RR 0.94 (0.84-1.04), p=0.22) or EGFR- TKIS (RR 1.42 (0.97-2.06), p=0.07).

However, sorafenib monotherapy was associated with statistically significant improvement in DCR compared with placebo (RR1.95 (1.59-2.39), p<0.00001), without heterogeneity among the studies (p=0.55, I^2=0%) (Figure 2).

Progression-Free Survival (PFS)

All 6 trial including 2748 patients provided PFS results. There was no significant difference between SBT

Table 1. Characteristic of the Six Eligible Randomized Trails in this Meta-analysis

Authors and year	Phase	Regimens (per arm)	Patients enrolled	Male (%)	Median age	Smoker (%)	Squamous (%)	ECOG PS 0 (%)
Wakelee et al 2012	II	Sor (400mg bid)	50	23 (46)	64.5	NR	6 (12.0)	21 (42)
		Placebo	31	18 (58)	69	NR	4 (12.9)	12 (39)
Paz-Ares et al 2012	III	Sor (400mg bid)	350	186 (53)	58.9	189 (54)	0 (0)	110 (31)
		Placebo	353	209 (59)	60.9	219 (62)	0 (0)	110 (31)
Spigel et al 2011	II	Sor (400mg bid)+Erl	111	62 (56)	65	92 (83)	33 (30)	32 (29)
		Placebo+Erl	55	26 (47)	65	47 (85)	17 (31)	16 (29)
Scagliotti et al 2010	III	Sor (400mg bid) +Car+Pac	464	293 (63)	62	388 (84)	109 (23)	190 (41)
		Placebo+ Car +Pac	462	288 (62)	63	397 (86)	114 (25)	188 (41)
Paz-Ares et al 2012	III	So r (400mg bid)+Gem+Cis	385	228 (59)	60	277 (72)	0 (0)	146 (38
		Placebo+Gem+Cis	387	245 (63)	58	287 (74)	0 (0)	143 (37)
Molina et al 2011	II	Sor (400mg bid)+Pem	49	28 (57)	62	NR	0 (0)	23 (47)
		Pem	51	23 (45)	62	NR	0 (0)	24 (47)

*ECOG PS, Eastern Cooperative Oncology Group performance status; Sor, Sorafenib; Erl, Erlotinib; Car, Carboplatin; Pac, Paclitaxel; Gem, Gemcitabine; Cis, Cisplatin; Pem, Pemetrexed; NR, No Report

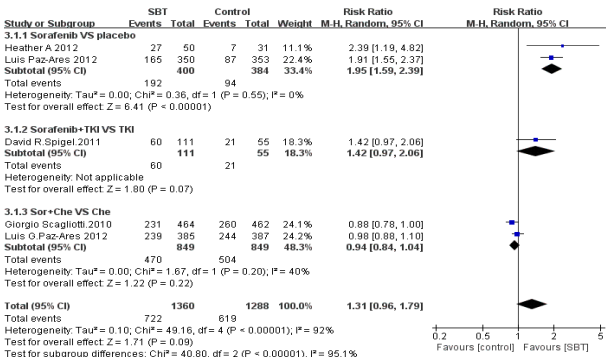

Figure 2. Comparison of DCR between SBT and Control Interventions (Random-Effects Model). SBT; Sorafenib-Based Therapy

and control arms regardless of trials designs (HR0.82 (0.66-1.02), p=0.07). Nevertheless, there might be substantial heterogeneity in the HRs for PFS from the individual trials (p=0.0001, I^2=80%) and we incorporated it into random-effects model. In terms of subgroup results, sorafenib monotherapy was associated with significant improvement in PFS (HR0.60 (0.51-0.70), p< 0.00001) without heterogeneity (p=0.54, I^2=0%). However, no significantly statistical difference in PFS was detected in combination with chemotherapy (HR0.95 (0.79-1.15), p=0.62) or EGFR-TKIS (HR0.86 (0.60-1.23), p=0.41) (Figure 3).

Overall Survival (OS)

There was no significant difference between SBT and control arms for the pooled HR for OS (HR1.01, 95% CI 0.92–1.12, P=0.77). There was no significant heterogeneity (p=0.32, I^2=14%) and the pooled HR for OS was performed using the fixed-effect model.

Results were similar when subgroup analyses were conducted. Statistically significant OS survival for SBT was not demonstrated regardless of sorafenib monotherapy (HR0.96, 95% CI 0.82–1.12, P=0.59), in combination with chemotherapy (HR1.06, 95% CI 0.94–1.20, p=0.33) or EGFR-TKI (HR0.89, 95% CI 0.59–1.34, p=0.58) (Figure 4).

Toxicities

This meta-analysis assessed the toxicities with grade

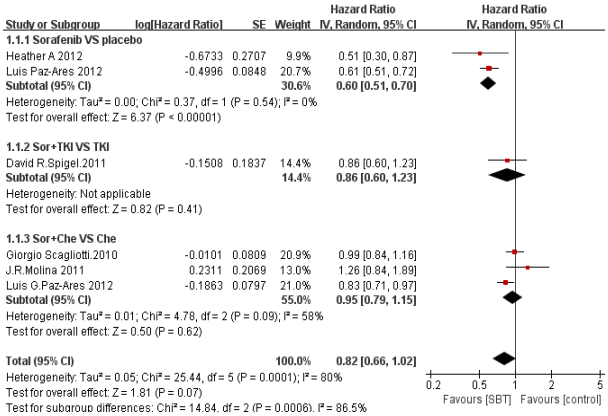

Figure 3. Comparison of PFS between SBT and Control Interventions (Random-Effects Model). SBT; Sorafenib-Based Therapy

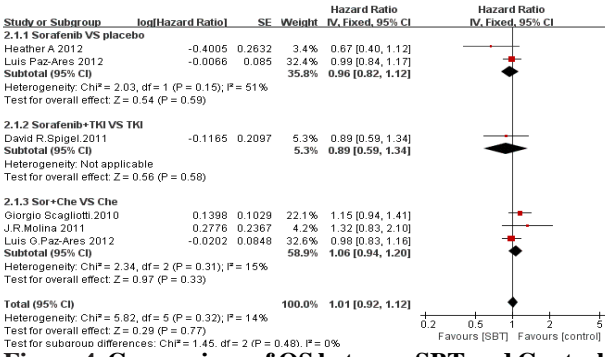

Figure 4. Comparison of OS between SBT and Control Interventions (Fixed-Effect Model). SBT; Sorafenib-Based Therapy

≥3 of SBT vs. control group. The analysis showed that the grade ≥3 sorafenib-related toxicities were fatigue (RR 1.74 (1.22–2.47), p=0.002) (p=0.82, I^2=0%), hypertension (RR3.05 (1.62–5.73), p=0.0005) (p=0.26, I^2=24%), diarrhea (RR2.70 (1.51-4.84), p=0.0008) (p=0.47, I^2=0%), oral mucositis (RR6.21 (1.85–20.82), p=0.003) (p=0.95, I^2=0%), rash (RR4.30 (2.54–7.29), p<0.00001) (p=0.0002, I^2=82%), and HFSR (RR14.41 (6.40–32.44), p<0.00001) (p=0.05, I^2=55%). The other toxicities including anemia (RR 0.88 (0.52–1.48), p=0.63) (p=0.53, I^2=0%), nausea (RR 0.78 (0.39–1.54), p=0.47) (p=0.47, I^2= 0%), neutropenia (RR 1.35 (0.97–1.87),

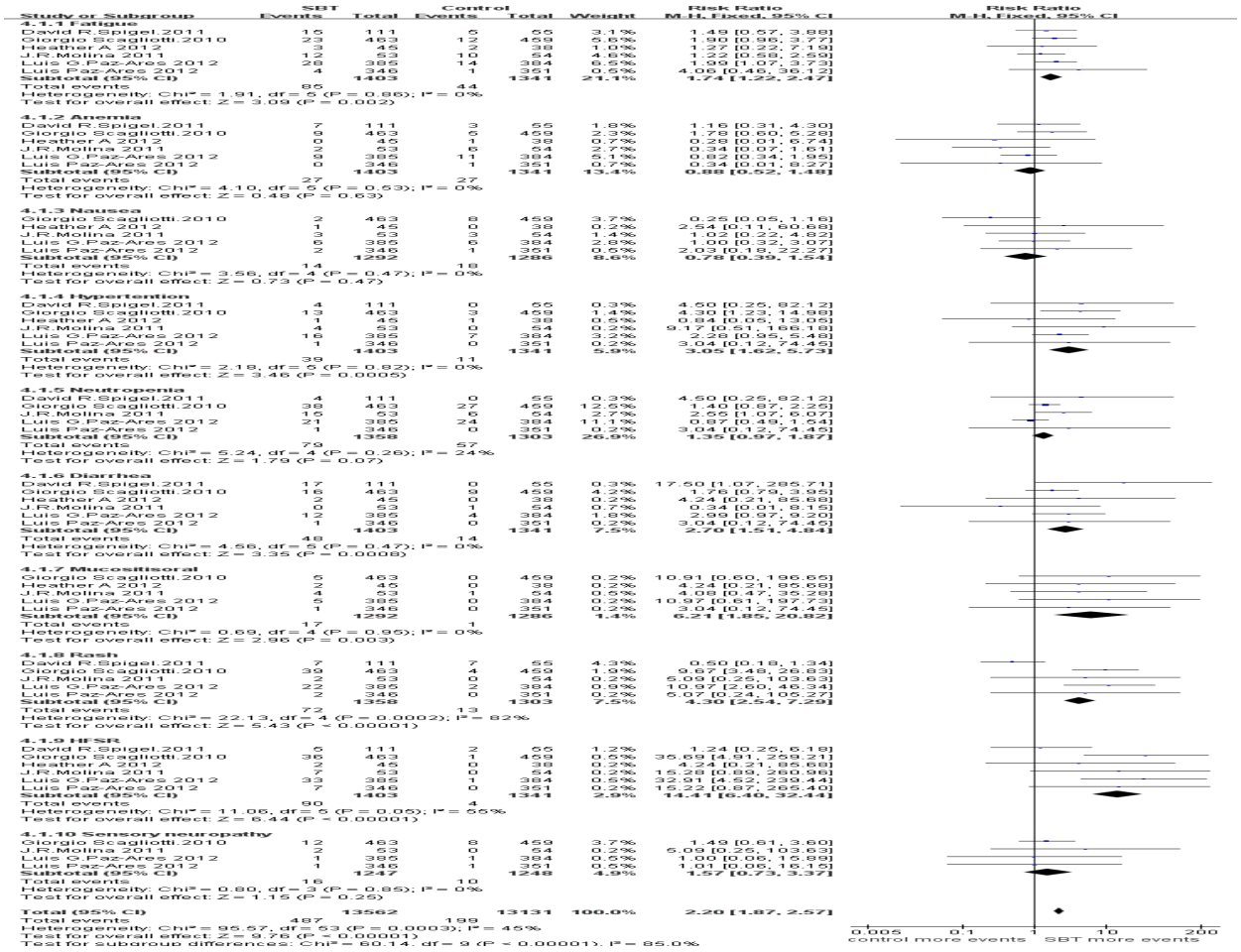

Figure 5. Comparison of Grade ≥3 Toxicities between SBT and control interventions. SBT; Sorafenib-Based Therapy

p=0.07) (p=0.26, I^2=24%) and sensory neuropathy (RR 1.57 (0.73–3.37), p=0.25) (p=0.85, I^2=0%) showed no statistically significant difference (Figure 5).

Publication bias

To minimize the publication bias, we selected papers strictly according to inclusion criteria. Furthermore, publication bias was detected by funnel plot. No Apparent publication bias according to the funnel plot for PFS and OS.

Discussion

Vascular endothelial growth factor (VEGF) signaling plays a major role in promoting the proliferation and differentiation of the endothelial cells (Carmeliet et al., 2000; Blau et al., 2001; Ferrara et al., 2005; Folkman et al., 2007). Others such as c-Raf, b-Raf, c-Kit and Flt3 are also key members of critical pathways for cell proliferation, differentiation and apoptosis (Kemmer et al., 2004; Kindler et al., 2010; Maurer et al., 2011; Berk et al., 2013). Sorafenib may have anti-tumor activities through a dual mechanism, acting indirectly on the tumor angiogenesis via VEGFR/PDGFR pathways and directly on tumor growth by inhibition Raf/Kit/Flt3 signaling (Wilhelm et al., 2008).

However, the results on the efficacy of several RCTs conducted to evaluate sorafenib in the treatment of advanced NSCLC are inconsistent. In the ESCAPE study, no clinical benefit was observed from sorafenib intercalated with carboplatin/ paclitaxel chemotherapy as first-line treatment (Scagliotti et al., 2010). In previously-treated NSCLC patients, sorafenib also failed to show additional benefits in combination with pemetrexed in a phase II trial (Molina et al., 2011). In a randomized, double-blind, placebo-controlled Phase II trial of sorafenib and erlotinib or erlotinib alone, sorafenib did not statistically improve DCR , PFS and OS when combined with erlotinib in patients with relapsed NSCLC (Spigel et al., 2011).

Nevertheless, another Phase III clinical trial NExUS still showed a clinically modest but statistically significant prolongation in progression-free survival for the sorafenib plus cisplatin/gemcitabine arm compared to cisplatin/ gemcitabine alone (6.1 versus 5.5 months, p<0.001) (Paz-Ares LG et al., 2012). In the MISSION trial of sorafenib monotherapy versus placebo as 3rd- or 4th-line treatment, the treatment with sorafenib improve DCR and PFS, but no improvement on OS (Paz-Ares L et al., 2012). In addition, a double-blind randomized discontinuation phase II study showed sorafenib improved DCR and PFS, and a trend in favor of overall survival with sorafenib was also observed compared with placebo (13.7 versus 9.0 months, p=0.117) (Wakelee et al., 2012). It was the inconsistency of these

results that motivated the present meta-analysis.

The results of our meta-analysis showed that SBT did not improve DCR, PFS and OS. Grade ≥3 toxicities increased with SBT were fatigue, hypertension, diarrhea, oral mucositis, rash and HFSR. Hence, existing evidence from randomized controlled trials does not support the use of sorafenib therapy for unselected administration of sorafenib and unselected patients with advanced NSCLC.

In terms of subgroup results, sorafenib combined with chemotherapy did not improve DCR, PFS and OS. Several factors may contribute to negative results in randomized trials of sorafenib in combination with chemotherapy in advanced NSCLC, including the choice of platinum-doublet regimen, the inclusion of patients with squamous cell carcinoma and administration sequence. One possible explanation for the negative results in the ESCAPE trail is that sorafenib could alter the pharmacokinetics of CP, thereby impairing the efficacy of the combined regimen compared with CP alone (Hauschild et al., 2009; Scagliotti et al., 2010). In the NExUS and NCCTG N0626 study, concomitant administration of sorafenib and chemotherapy may impact the efficacy of sorafenib in advanced non-small cell lung cancer (Molina et al., 2011; Paz-Ares LG et al., 2012). Sorafenib inhibits tumor growth by inducing G1 cell cycle arrest, thus potentially interfering with the cycle-dependent toxicity of chemotherapy when this is administered concomitantly (Plastaras et al., 2007; Takezawa et al., 2009; Li et al., 2013). However, the NExUS trial still showed a clinically modest but statistically significant PFS. Apparently, both curves clearly separated past six months since treatment initiation, suggesting that sorafenib given as single agent after 6 cycles followed by maintenance therapy was associated with a certain degree of clinical activity (Metro et al., 2012).

Subgroup analysis showed that sorafenib as monotherapy significantly improved the DCR and PFS, but the improved DCR and PFS did not lead to a prolonged OS. Although the two trails did not meet its primary endpoint of OS, median PFS was 84 days for sorafenib versus 43 days for placebo (p<0.0001), and DCR was 47% versus 25% (p<0.0001) in the MISSION trail (Paz-Ares L et al., 2012). And in the study E2501, median PFS was 3.3 months for sorafenib versus 2.0 months for placebo (p=0.014), and DCR was 54% versus 23% (p=0.005) (Wakelee et al., 2012). Although MISSION and study E2501 were placebo-controlled trails, some of the patients received post-study treatment , which might have negative impacted on the OS data (Wakelee et al., 2012; Blumenschein et al., 2013). In addition , PFS but not OS is usually selected as the primary endpoint as it may provide a direct measurement of the effect of the therapy on the tumor, and slowing disease progression may also slow symptom progression, leading to an important palliative benefit.

In the result of sorafenib combine erlotinib, the treatment inhibiting both VEGFR and EGFR signaling pathways does not improve DCR, PFS and OS among unselected patients. However, subset analyses by Spigel et al. in the trail showed a benefit in EGFR WT and EGFR FISH-negative patients for the combination of erlotinib/sorafenib compared with single-agent erlotinib with respect to PFS and OS (Spigel et al., 2011). Similarly, a multicenter phase II study of erlotinib and sorafenib in chemotherapy-naive patients with advanced non-small cell lung cancer also suggested that patients with wild-type EGFR had a higher ORR than previously reported for single-agent erlotinib/sorafenib (Lind et al., 2010). One potential explanation for this finding may be that EGFR-mutant disease is best targeted by EGFR inhibitors, but EGFR WT tumors are more dependent on other signaling pathways, including VEGFR, Raf, or platelet- derived growth factor receptor, which are inhibited by sorafenib. This indicates that further study of sorafenib combine erlotinib in EGFR mutation-negative patients is warranted.

As expected, some toxicity was significantly more severe in patients who received SBT therapy. Grade ≥3 toxicities increased with SBT were fatigue, hypertension, diarrhea, oral mucositis, rash and HFSR. However, in general, these side effects were manageable.

There are several limitations in the present meta-analysis. First, data extracted from the literature, treatment with sorafenib-based therapy was considered to be the experimental arm and sorafenib-free therapy was considered to be the control arm. However, SBT varies in these trails, including first-line sorafenib intercalated with carboplatin/paclitaxel, first-line concomitant administration of sorafenib with cisplatin/gemcitabine, second-line sorafenib combine pemetrexed, multi-line sorafenib monotherapy and second-line or third-line sorafenib plus erlotinib. Different platinum-doublet regimen, administration sequence, sorafenib in combination other therapy or sorafenib montherapy resulted in different efficacy and toxicities in patients. Although subgroup analysis was performed to investigate possible optimum therapy strategy, the small number of the trials limited the power of the analysis. Second, heterogeneity among trials can be another limitation of our meta-analysis. We applied a random effect model that takes possible heterogeneity into consideration. Third, we did not analyze the relationship between biomarkers and sorafenib outcome because of the low number of RCTs and patients. Further, one study we identified was reported in an abstract form only, which data about DCR was not offered in the abstract, though this study was unlikely to change the overall results because of its small sample size.

In general, SBT did not improve the DCR, PFS and OS, Grade ≥3 toxicities such as fatigue, hypertension, diarrhea, oral mucositis, rash and HFSR in SBT group was higher compared with control arms. However, we found sorafenib as monotherapy showed some activity in NSCLC according to subgroup analysis, some of patients in the placebo-controlled trials received post-study treatment might have negative impacted on the OS data. Therefore, sorafenib monotherapy may be considered for further evaluation in subsets of patients who may benefit from this treatment. Sorafenib combined inhibition therapy should be limited unless the choice of platinum-doublet regimen, administration sequence or identification of predictive biomarkers were considered to receive better anti-tumor activity and prevention of resistance mechanisms.

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