

## RESEARCH ARTICLE

# Risk of Treatment-related Mortality with Sorafenib in Patients with Cancer

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### Abstract

**Background:** Fatal adverse events (FAEs) have been reported with sorafenib, a vascular endothelial growth factor receptor kinase inhibitor (VEGFR TKI). We here performed an up-to-date and detailed meta-analysis to determine the overall risk of FAEs associated with sorafenib. **Methods:** Databases, including PubMed, Embase and Web of Science, and abstracts presented at the American Society of Clinical Oncology annual meetings were searched to identify relevant studies. Eligible studies included randomized controlled trials evaluating sorafenib effects in patients with all malignancies. Summary incidence rates, relative risks (RRs), and 95% confidence intervals (CIs) were calculated for FAEs. In addition, subgroup analyses were performed according to tumor type and therapy regimen. **Results:** 13 trials recruiting 5,546 patients were included in our analysis. The overall incidence of FAEs with sorafenib was 1.99% (95% CI, 0.98-4.02%). Patients treated with sorafenib had a significantly increased risk of FAEs compared with patients treated with control medication, with an RR of 1.77 (95% CI 1.25-2.52,  $P=0.001$ ). Risk varied with tumour type, but appeared independent of therapy regimen. A significantly increased risk of FAEs was observed in patients with lung cancer (RR 2.26; 95% CI 1.03-4.99;  $P=0.043$ ) and renal cancer (RR 1.84; 95% CI 1.15-2.94;  $P=0.011$ ). The most common causes of FAEs were hemorrhage (8.6%) and thrombus or embolism (4.9%). **Conclusions:** It is important for health care practitioners to be aware of the risks of FAEs associated with sorafenib, especially in patients with renal and lung cancer.

**Keywords:** Sorafenib - epidermal growth factor receptor-2 - fatal adverse events - mortality - meta-analysis

*Asian Pac J Cancer Prev*, 14 (11), 6681-6686

### Introduction

Vascular endothelial growth factor (VEGF)-targeted therapies improve clinical outcomes in several malignancies and have become a cornerstone in the treatment of many cancers. Sorafenib is a small molecule targeting the intracellular tyrosine kinase (TK) domain of the VEGF receptor (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 (Wilhelm et al., 2004). In phase II and phase III randomised trials, sorafenib significantly prolonged progression-free survival as compared with placebo in patients with metastatic renal-cell carcinoma (Ratain et al., 2006; Escudier et al., 2007).

Additionally, sorafenib was shown to be efficacious and well-tolerated in patients with advanced hepatocellular carcinoma in randomized controlled trails (RCTs) (Abou-Alfa et al., 2006; Llovet et al., 2008).

Based on these results, sorafenib has been approved

by the US Food and Drug Administration (FDA) for treatment of renal cell cancer (RCC) and hepatocellular cancer (HCC) (Escudier et al., 2009; Printz 2009).

Furthermore, clinical efficacy was also found for sorafenib in phase II clinical trials for other malignant diseases such as advanced melanoma, breast cancer, non-small cell lung cancer, urothelial cancer, prostate cancer, carcinoma of the head and neck, gastrointestinal stromal tumours and thyroid cancer.

With the wider usage in clinical practice, side-effects of sorafenib began to be recognized and some of which may be potentially life threatening, such as congestive heart failure (CHF), arterial thrombosis, wound dehiscence, haemorrhage, hypertension, and renal dysfunction (Chu et al., 2008; Wu et al., 2008; Chu et al., 2009; Je et al., 2009; Kerkela et al., 2009; Choueiri et al., 2010; Ewer et al., 2010; Hutson et al., 2010).

Fatal adverse events (FAEs) are deaths that related to use of the pharmaceutical agent. Although the incidence of such complications is low, knowing that is important for planning adequate strategies to limit their effect. Recently, two meta-analyses have shown a significant increase in

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FAEs with VEGFR TKIs including sorafenib, sunitinib, pazopanib, and vandetanib (Schutz et al., 2012; Sivendran et al., 2012).

In the subgroups analyses of the four VEGFR TKIs, only sorafenib reached a statistical significance. These findings have shed light on the risk of increased FAEs induced by sorafenib, however, these reports were based on a limited number of trials, and did not include the RCTs of breast cancer published subsequently. Some important questions remain to be answered and deserve further evaluation. Whether the association of sorafenib and the risk of FAES varied significantly with tumor types and therapy regimen is still unclear. Another important issue involves major cause of FAES with sorafenib which may offer additional insights into early and adequate intervention or prevention. To take account of the expanded evidence base and address the issues above, we conducted a detailed and updated meta-analysis with RCTs published in latest literature.

## Materials and Methods

### Data source

We performed this meta-analysis according to the QUORUM guidelines (Quality of Reporting of Meta-analyses). The keywords “sorafenib”, “cancer” and “carcinoma” were used to search citations from PubMed and Embase until April, 2013. The publications were limited in randomized controlled trials. The annual meeting proceedings of American Society of Clinical Oncology (ASCO) and European Society of Medical Oncology (ESMO) from 2004 to 2013 were hand searched for relevant randomised clinical trials. An independent search of relevant reviews and meta analyses regarding sorafenib was also done to ensure that no studies were missed. Two reviewers (Feifei Yu and Tianyi Zhang) independently reviewed each publication. If the relevant data were not clear or easy to misunderstand, efforts were paid to contact the authors of those studies.

### Study selection

Studies that meet the following criteria were included, that is: 1) prospective phase II and III trials of sorafenib in the treatment of patients with cancer 2) random assignment of patients to sorafenib or placebo/best supportive care with or without concurrent chemotherapy and/or biological agent.

### Quality assessment and Data extraction

Quality assessment and data abstraction were conducted independently by two reviewers (Feifei Yu and Tianyi Zhang) using a standardized approach. Quality of studies included in this meta-analysis were assessed with the Jadad Score (Jadad et al., 1996). The trials with a score of 3 or above are regarded as high quality.

The basic data of the studies including publication details, trial characteristics, treatment information, and survival outcomes were retrieved. Meanwhile, the fatal adverse event, defined as deaths related to adverse events as reported according to the National Cancer Institute's Common Terminology Criteria for Adverse Events

(CTCAE) criteria (version 3) (2006), was the primary end point of the analysis. Number of patients available for safety analysis, number of fatal adverse events, and adverse event type were extracted from the safety profile of each study. We excluded FAEs that were reported as unrelated to study drug.

### Statistical analysis

We used the number of FAEs and the number of patients receiving therapy to calculate the Incidence and the corresponding 95% CI. Pooled risk ratio (RR) and its 95% CIs of FAEs in patients assigned to sorafenib versus those given placebo or best supportive care were estimated by Mantel and Haenszel method (Deeks et al., 2008). An  $RR > 1$  indicates a higher risk of FAEs in the sorafenib arm. We also did the subgroup analysis by tumor type and therapy regimen. Statistical significance was defined as a two-tailed p-value less than 0.05. All of the statistical analyses were conducted in Comprehensive Meta Analysis software (version 2).

The heterogeneity among studies were evaluated by the  $\chi^2$  test and  $I^2$ . high-level heterogeneity would be defined if the  $I^2$  were 25% and more or the p-value for  $\chi^2$  test were less than 0.1. If the result of heterogeneity test is not significant, a fixed-effect model will be performed, or a random-effect model was employed. In addition, Egger's test (Egger et al., 1997) and Begg-Mazumdar test (Begg et al., 1994) were implemented to detect the publication bias.

## Results

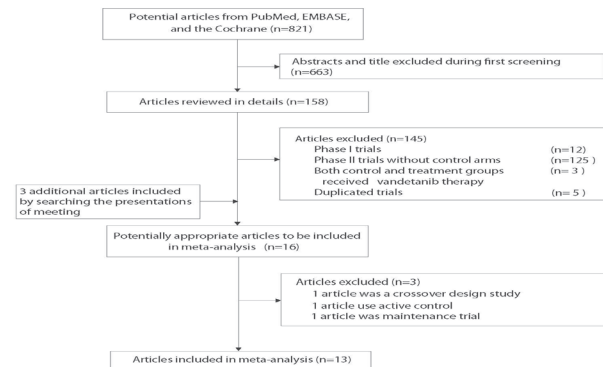
A total of 821 abstracts were reviewed, and 18 of them were defined as eligible trials which discussed the treatment effect and safety of sorafenib versus placebo or best supportive care. Of these 18 articles, one was a crossover design study (Escudier et al., 2009), one used active control (Rini et al., 2011), one article was an economical assessment (Muszbek et al., 2008) and two articles studied biomarkers (Galal et al., 2011; Kim et al., 2011), so that they were excluded.

Therefore, there were 13 articles that met our inclusion criteria with 2838 patients in sorafenib group and 2708 patients in control group. Four trials (Escudier et al., 2007; Llovet et al., 2008; Cheng et al., 2009; Kudo et al., 2011) assessed sorafenib as single agent whereas the other nine trials (McDermott et al., 2008; Hauschild et al., 2009; Abou-Alfa et al., 2010; Scagliotti et al., 2010; Spigel et al., 2011; Wang et al., 2011; Baselga et al., 2012; Paz-Ares et al., 2012; Flaherty et al., 2013) assessed sorafenib in combination with concurrent chemotherapy and/or biological agent. Underlying malignancies included breast cancer (one study) (Baselga et al., 2012) NSCLC (four studies) (Scagliotti et al., 2010; Spigel et al., 2011; Wang et al., 2011; Paz-Ares et al., 2012), hepatocellular carcinoma (four studies) (Llovet et al., 2008; Cheng et al., 2009; Abou-Alfa et al., 2010; Kudo et al., 2011), melanoma (three studies) (McDermott et al., 2008; Hauschild et al., 2009; Flaherty et al., 2013) and renal-cell carcinoma (one study) (Escudier et al., 2007). All of the articles were assessed by the Jadad Score and scored three or more.

**Table 1. Characteristics of the Trials Included in the Final Analysis**

Source	Phase	Cancer	Treatment arm	No. of Patients Enrolled	No. of Patients Analyzed	Median age	Male (%)	Median PFS(month)	Median OS (month)	FAE	Jadad Score
Flaherty 2013	3	Metastatic Melanoma	Carboplatin+Paclitaxel	413	397	59	61	4.2	11.3	8	3
			Carboplatin+Paclitaxel+ Sorafenib	410	393	61	66	4.9	11.1	9	
Paz-Ares 2012	3	NSCLC	Sorafenib+GC	385	385	60	59.2	6.0	12.4	5	3
			Placebo+GC	387	384	58	63.3	5.5	12.5	2	
Baselga 2012	2	Breast Cancer	Sorafenib+Capecitabine	115	112	55.1	0	6.4	22.2	0	4
			Placebo+Capecitabine	114	112	54.4	0.9	4.1	20.9	2	
Wang 2011	NA	NSCLC	Gem+Cis+Sorafenib	18	18	54	55.6	5	18	1	3
			Gem+Cis+Placebo	12	12	56	58.3	4	18	0	
Spigel 2011	2	NSCLC	Sorafenib+Erlotinib	111	111	65	56	3.38	7.62	0	4
			Placebo+Erlotinib	55	55	65	47	1.94	7.23	1	
Abou-Alfa 2010	2	HCC	Doxorubicin+Sorafenib	47	47	66	66	6.0	13.7	3	5
			Doxorubicin+Placebo	49	48	65	85.7	2.7	6.5	2	
Hauschild 2009	3	Melanoma	Placebo+CP	135	134	56	64	4.5	NA	0	4
			Sorafenib+CP	135	134	57	62	4.4	NA	4	
Cheng 2009	3	HCC	Sorafenib	150	149	51	84.7	2.8	6.5	0	4
			placebo	76	75	52	86.8	1.4	4.2	0	
Llovet 2008	3	HCC	Sorafenib	299	297	64.9	87	4.1	10.7	0	4
			Placebo	303	302	66.3	87	4.9	7.9	0	
Escudier 2007	3	RCC	Sorafenib	451	451	58	70	5.5	19.3	46	4
			Placebo	452	451	59	75	2.8	15.9	25	
Scagliotti 2010	3	NSCLC	Sorafenib +CP	464	463	62	63	4.6	10.7	13	3
			CP	462	459	63	62	5.4	10.6	4	
McDermott 2008	2	Melanoma	Placebo+Dacarbazine	50	50	60	66	2.9	12.8	0	4
			Sorafenib +Dacarbazine	51	51	55	91	5.3	11.4	0	
Kudo 2011	3	HCC	Sorafenib	229	227	69	76	5.4	29.7	0	3
			placebo	229	229	70	73.4	3.7		0	

NA, data not available; NSCLC, non-small cell lung cancer; HCC, hepatocellular carcinoma; RCC, renal-cell carcinoma; CP, carboplatin and paclitaxel; GC, gemcitabine and cisplatin

**Figure 1. Flow Diagram of the Trials Search and Selection Process**

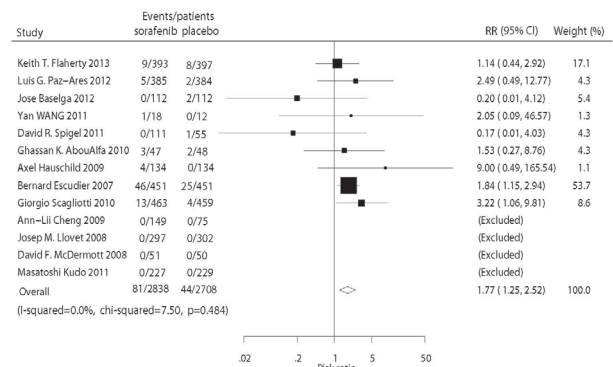
### Incidence of FAEs

The incidence of FAEs in sorafenib group was 1.99% (95%CI, 0.98%-4.02%) among 2838 patients. For the control group in which patients received placebo with or without supportive chemotherapy, the incidence of FAEs was 1.42% (95%CI, 0.72%-2.77%) among 2708 patients.

### Relative Risk of FAEs

Nine randomized studies including 4166 patients were available to calculate the relative risk of FAEs of sorafenib as compared with placebo.

Compared with controls, the relative risk of FAEs associated with sorafenib was 1.77 (95%CI 1.25-2.52; incidence, 1.99% vs 1.42%). There was no significant heterogeneity among the individual trials ( $P = 0.484$ ;  $I^2 = 0.0\%$ ) (Figure 2), and no evidence of significant

**Figure 2. The Comparison of FAEs Between Sorafenib and Control Group**

publication bias was detected (Egger test,  $P = 0.064$ ; Begg-Mazumdar test,  $P = 0.462$ ). Thus, these results provided additional evidence that sorafenib could significantly increase risk of FAEs in patients with cancer.

### Risk of FAEs by Tumor Type

Patients with different tumors might be at different risks of FAEs, due to differences in tumor biology and associated treatment. We determined whether having a specific type of cancer is associated with a higher risk for FAEs compared with other cancers. As shown in Table 1, an increased risk of FAEs with sorafenib was found in patients with NSCLC (RR 2.26; 95% CI 1.03-4.99;  $P = 0.043$ ), renal cancer (RR 1.84; 95% CI 1.15-2.94;  $P = 0.011$ ), melanoma (RR 1.60; 95% CI 0.68-3.75;  $P = 0.278$ ) and hepatocellular cancer (RR 1.53; 95% CI 0.27-

**Table 2. Incidence and Relative Risk (RR) of FAEs with Sorafenib According to Cancer Type and Drug Type**

	No. of Studies	No. of FAEs/Total Participants		Incidence of FAEs, % (95% CI)		RR (95% CI)
		Trastuzumab	Control	Sorafenib	Control	
<b>Tumor type</b>						
NSCLC	4	19/977	7/910	2.27 (1.46-3.51)	0.92 (0.45-1.88)	2.26 (1.03-4.99)
Melanoma	3	13/578	8/581	2.40 (1.41-4.05)	1.76 (0.92-3.35)	1.60 (0.68-3.75)
HCC	4	3/720	2/654	0.68 (0.07-5.87)	0.75 (0.13-4.22)	1.53 (0.27-8.76)
RCC	1	46/451	25/451	10.2 (7.73-13.35)	5.54 (3.77-8.07)	1.84 (1.15-2.94)
Breast Cancer	1	0/112	2/112	0.44 (0.03-6.67)	1.79 (0.45-6.86)	0.20 (0.01-4.12)
<b>Drug type</b>						
Sorafenib alone	4	46/1124	25/1057	0.75 (0.05-10.59)	0.79 (0.09-6.60)	1.84 (1.15-2.94)
Drug combination	9	35/1714	19/1651	2.46 (1.78-3.39)	1.51 (0.98-2.32)	1.70 (1.00-2.87)
Overall	13	81/2838	44/2708	1.99 (0.98-4.02)	1.42 (0.72-2.77)	1.77 (1.25-2.52)

NSCLC, non-small-cell lung cancer; HCC, hepatocellular carcinoma; RCC, renal-cell carcinoma

**Table 3. Fatal Adverse Events by Specific Type**

Type of AE	Events on sorafenib arm	Events on control arm	Number of Studies
Hemorrhage	7	3	3
Embolism or thrombus	4	2	4
Cardiotoxicity	3	2	2
Neutropenic sepsis	2	0	1
Respiratory failures	2	0	1
Respiratory insufficiency	1	0	1
Dyspnea	1	0	1
Cerebral edema	1	0	1
Liver dysfunction	1	0	1
Gastro-intestinal perforation	1	0	1
Pneumonitis	1	0	1
Renal failure	1	0	1
Diarrhea	0	1	2
Constitutional (other)	0	1	1
Not specified	56	35	3
Total	81	44	9

8.76;  $P=0.632$ ), but not in patients with breast cancer (RR 0.20; 95% CI 0.01-4.12;  $P=0.297$ ). Among the tumors with increased risk of FAEs, the highest incidence of FAEs was observed in patients with renal cancer (10.20%, 95% CI 7.73-13.35). And the relative risk of FAEs was highest in patients with NSCLC treated with sorafenib as compared with controls (relative risk 2.26, 95% CI 1.03-4.99). These results suggested that the risk of FAEs associated with sorafenib varied according to tumor type.

#### Risk of FAEs by Sorafenib Regimen

To further understand the role of sorafenib in the development of FAEs in cancer patients, we assessed whether combination with other therapy may alter the risk of FAEs. From 4 trials (Escudier et al., 2007; Llovet et al., 2008; Cheng et al., 2009; Kudo et al., 2011) containing 4858 patients (heterogeneity test:  $Q=6.25$ ,  $P=0.79$ ,  $I^2=0.001$ ), sorafenib as single agent was associated with a significantly increased risk of FAEs with an RR of 1.31 (95% CI, 1.02-1.68;  $P=.04$ , Table 2). From 9 trials (McDermott et al., 2008; Hauschild et al., 2009; Abou-Alfa et al., 2010; Scagliotti et al., 2010; Spigel et al., 2011; Wang et al., 2011; Baselga et al., 2012; Paz-Ares et al., 2012; Flaherty et al., 2013) containing 3594 patients (heterogeneity test:  $Q=4.97$ ,  $P=0.55$ ,  $I^2=0.001$ ), sorafenib in combination with other therapy was associated with a significantly increased risk of FAEs with an RR of 1.31 (95% CI, 1.08-1.60;  $P=0.007$ , Table 3). Thus, both the regimens of sorafenib were associated with a significantly increased risk of FAEs.

#### Causes of FAEs

Among the total of 81 FAEs with sorafenib therapy, 25 (30.9%) had specified causes attributable to the death. Of the specified FAEs, hemorrhage ( $n=7$ , 8.6%) was one of the most frequently occurring FAEs. Another important FAE was embolism or thrombus, which representing a total of four deaths (4.9%) of all study deaths associated with sorafenib. Other less frequent FAEs were cardiotoxicity ( $n=3$ ), cerebral edema ( $n=1$ ), neutropenic sepsis ( $n=2$ ), Respiratory failures ( $n=2$ ), Respiratory insufficiency ( $n=1$ ), Dyspnea ( $n=1$ ), gastro-intestinal perforation ( $n=1$ ), liver dysfunction ( $n=1$ ), pneumonitis ( $n=1$ ), renal failure ( $n=1$ ).

#### Discussion

The contribution of sorafenib to the development of FAEs is difficult to assess as the incidence of FAEs is relatively low in an individual trial and a single RCT is not powered to detect a significant relationship. Meta-analysis is a powerful statistical tool that overcomes this limitation by identifying, appraising, synthesizing, and aggregating relevant clinical studies. Based on 13 RCTs, our analysis showed a significantly increased risk of FAEs with the use of sorafenib compared with controls (RR 1.77; 95% CI 1.25-2.52;  $P=0.001$ ). Given the widely use of sorafenib in cancer patients, it is important to understand and recognize the risk of FAEs with sorafenib therapy and perform early prevention.

To date, there have been three meta-analyses to implicate the inhibition of the VEGF pathway with an increased risk of FAEs in patients with cancer (Ranpura et al., 2011; Schutz et al., 2012; Sivendran et al., 2012). One evaluated the risk of FAEs with the anti-VEGF monoclonal antibody bevacizumab (Ranpura et al., 2011). The other two (Schutz et al., 2012; Sivendran et al., 2012) accessed VEGFR TKI therapy (including Sunitinib, Sorafenib, Pazopanib and Vandetanib), of which, the subgroup analysis shed light on the association of FAEs with sorafenib. After including additional six RCTs, our study directly demonstrated sorfenib increased the risk of FAEs in patients with cancer, which added further validity of the previous findings.

In our study, hemorrhage and thrombus or embolism were observed to be the most common cause of specified FAEs. It may be related to the disruption of endothelial cells caused by inhibiting VEGFR (Byrne et al., 2005; Sonpavde et al., 2012). Endothelial cells play a critical role

in maintaining the integrity of vascular wall (Kamba et al., 2007), in preventing abnormal bleeding, abnormal blood clotting (Esmon, 1987) and in producing nitric oxide (NO) which has several vascular protective effects, including antiplatelet actions and inhibition of leukocyte inhibition (Shen et al., 1999; Zachary et al., 2001; Gonzalez-Pacheco et al., 2006). As a result, the VEGF signaling inhibitor, sorafenib, renders patients more susceptible to bleeding and thrombus or embolism. Therefore, special attention should be paid to hemorrhage and embolism or thrombus during the treatment of sorafenib.

We included patients with a variety of different solid tumors and the risk of FAEs with sorafenib may potentially vary with tumor types. In the patients with renal and lung cancer, the relative risk of FAEs with sorafenib reached statistical significance. This finding is consistent with the results in previous studies (Schutz et al., 2012; Sivendran et al., 2012), in which, lung and renal cancer are considered to be the risk factors of FAEs associated with VEGFR-TKIs. Hence, patients with lung and renal cancer warrant more careful and continued surveillance when treated with sorafenib therapy. Among all of the subgroups, sorafenib was not observed to increase the risk of FAEs only in patients with breast cancer. This might be due to pathogenesis of malignancy, synergic effect of concurrent chemotherapy and spectrum of patient comorbidity. However, there was only one trial breast cancer included in this study, so the results should be interpreted with caution.

We also evaluated associations of sorafenib with FAEs according to the regimen of therapy. A significantly increased risk of FAEs was observed no matter sorafenib used as single agent or combined with other chemotherapy and the risk was similar between the two groups (RR: single, 1.84 combination, 1.70). This finding indicates that the increased risk of FAEs with sorafenib is independent of the regimen of therapy.

For patients receiving sorafenib, careful monitoring and stopping rules in the clinical trial setting are needed to reduce the risk of death related to these toxicities. Physicians should be highly vigilant to detect any signs of FAEs, especially of hemorrhage and thrombus or embolism. Additionally, tumor type should also be an important consideration when sorafenib is applied in patients with cancer.

There are several limitations in our study. First, these studies were conducted at various institutions by different investigators internationally. FAEs were not the primary endpoint of any of the included studies and determining whether a FAE is attributable to sorafenib therapy is associated with some subjectivity. Therefore, there may be some potential bias in reported incidences or specification of FAEs. Second, all of the included studies were conducted in patients with adequate major organ function at study entry so the actual incidence and risk of FAEs may be underestimated in general populations in the community and in the setting of organ dysfunction. Thirdly, there were a relatively large number of unspecified causes of FAEs (almost 70%) that occurred in association with sorafenib use. The inability to fully characterize the cause of fetal events may lead to loss of some information. Further studies are needed to elucidate the precise causes of FAEs, which might also allowed development of strategies to mitigate

risk. Finally, this is a meta-analysis at study level, and confounding variables at patient level cannot be assessed properly and incorporated into the analysis. However, a review by Bennett et al. (2008) showed that the results between patient and study level were remarkably similar.

In summary, this study demonstrates that sorafenib is associated with an increased risk of FAEs in patients with cancer. The increased risk of FAEs associated with sorafenib may vary with tumor type but is independent of regimen of therapy. It is important for health care practitioners to be aware of the risks as well as the benefits associated with sorafenib and to provide close monitoring to improve patient outcomes.

## Acknowledgements

This research is supported by the grants from the key discipline construction of evidence-based public health in Shanghai (NO. 12GWZX0602), The Ministry of Science and Technology of China (Project Nos. 81072388 and 81373105). All of the authors agreed with the submission of the article. The authors thank all of the patients involved in this trial and all investigators who contributed to study development. Furthermore, the authors would like to thank Prof. Bang for providing very detailed information on the FAEs occurring in (the) ToGA trial which is considerably helpful and substantially improved this manuscript. The author (s) declare that they have no competing interests.

## References

- Abou-Alfa GK, Johnson P, Knox JJ, et al (2010). Doxorubicin plus sorafenib vs doxorubicin alone in patients with advanced hepatocellular carcinoma: a randomized trial. *JAMA*, **304**, 2154-60.
- Abou-Alfa GK, Schwartz L, Ricci S, et al (2006). Phase II study of sorafenib in patients with advanced hepatocellular carcinoma. *J Clin Oncol*, **24**, 4293-300.
- Baselga J, Segalla JG, Roche H, et al (2012). Sorafenib in combination with capecitabine: an oral regimen for patients with HER2-negative locally advanced or metastatic breast cancer. *J Clin Oncol*, **30**, 1484-91.
- Begg CB, Mazumdar M (1994). Operating characteristics of a rank correlation test for publication bias. *Biometrics*, **50**, 1088-101.
- Bennett CL, Silver SM, Djulbegovic B, et al (2008). Venous thromboembolism and mortality associated with recombinant erythropoietin and darbepoetin administration for the treatment of cancer-associated anemia. *JAMA*, **299**, 914-24.
- Byrne AM, Bouchier-Hayes DJ, Harme JH (2005). Angiogenic and cell survival functions of vascular endothelial growth factor (VEGF). *J Cell Mol Med*, **9**, 777-94.
- 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.
- Choueiri TK, Schutz FA, Je Y, Rosenberg JE, Bellmunt J (2010). Risk of arterial thromboembolic events with sunitinib and sorafenib: a systematic review and meta-analysis of clinical trials. *J Clin Oncol*, **28**, 2280-5.
- Chu D, Lacouture ME, Fillos T, Wu S (2008). Risk of hand-foot skin reaction with sorafenib: a systematic review and meta-analysis. *Acta Oncol*, **47**, 176-86.
- Chu D, Lacouture ME, Weiner E, Wu S (2009). Risk of hand-foot skin reaction with the multitargeted kinase inhibitor sunitinib in patients with renal cell and non-renal cell carcinoma: a meta-analysis. *Clin Genitourin Cancer*, **7**, 11-9.

- Deeks JJ, Higgins J, Altman DG (2008). Analysing Data and Undertaking Meta-Analyses. *Cochrane Handbook for Systematic Reviews of Interventions: Cochrane Book Series*, 243-96.
- Egger M, Smith GD, Schneider M, Minder C (1997). Bias in meta-analysis detected by a simple, graphical test. *BMJ*, **315**, 629-34.
- Escudier B, Eisen T, Stadler WM, et al (2007). Sorafenib in advanced clear-cell renal-cell carcinoma. *N 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.
- Escudier B, Szczylik C, Hutson TE, et al (2009). Randomized phase II trial of first-line treatment with sorafenib versus interferon Alfa-2a in patients with metastatic renal cell carcinoma. *J Clin Oncol*, **27**, 1280-9.
- Esmon CT (1987). The regulation of natural anticoagulant pathways. *Science*, **235**, 1348-52.
- Ewer MS, Suter TM, Lenihan DJ, et al (2010). Cardiovascular adverse events (CV-AES) in a pooled analysis of 1090 patients (PT) from phase 3 sunitinib (SU) trials. 35th European Society for Medical Oncology. Milan, Italy, 506.
- Flaherty KT, Lee SJ, Zhao F, et al (2013). Phase III trial of carboplatin and paclitaxel with or without sorafenib in metastatic melanoma. *J Clin Oncol*, **31**, 373-9.
- Galal KM, Khaled Z, Mourad AM (2011). Role of cetuximab and sorafenib in treatment of metastatic colorectal cancer. *Indian J Cancer*, **48**, 47-54.
- Gonzalez-Pacheco FR, Deudero JJ, Castellanos MC, et al (2006). Mechanisms of endothelial response to oxidative aggression: protective role of autologous VEGF and induction of VEGFR2 by H2O2. *Am J Physiol Heart Circ Physiol*, **291**, H1395-401.
- Hauschild A, Agarwala SS, Trefzer U, et al (2009). Results of a phase III, randomized, placebo-controlled study of sorafenib in combination with carboplatin and paclitaxel as second-line treatment in patients with unresectable stage III or stage IV melanoma. *J Clin Oncol*, **27**, 2823-30.
- Hutson T, Procopio G, Escudier B, et al (2010). Long-term sorafenib (SOR) safety profile in more than 700 patients (pts) with renal-cell carcinoma (RCC) treated for 12 to 42 months (mos). *J Clin Oncol* (Meeting Abstracts).
- Jadad AR, Moore RA, Carroll D, et al (1996). Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*, **17**, 1-12.
- Je Y, Schutz FA, Choueiri TK (2009). Risk of bleeding with vascular endothelial growth factor receptor tyrosine-kinase inhibitors sunitinib and sorafenib: a systematic review and meta-analysis of clinical trials. *Lancet Oncol*, **10**, 967-74.
- Kamba T, McDonald DM (2007). Mechanisms of adverse effects of anti-VEGF therapy for cancer. *Br J Cancer*, **96**, 1788-95.
- Kerkela R, Woulfe KC, Durand JB, et al (2009). Sunitinib-induced cardiotoxicity is mediated by off-target inhibition of AMP-activated protein kinase. *Clin Transl Sci*, **2**, 15-25.
- Kim ES, Herbst RS, Wistuba II, et al (2011). The BATTLE trial: personalizing therapy for lung cancer. *Cancer Discov*, **1**, 44-53.
- 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.
- Llovet JM, Ricci S, Mazzaferro V, et al (2008). Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*, **359**, 378-90.
- McDermott DF, Sosman JA, Gonzalez R, et al (2008). Double-blind randomized phase II study of the combination of sorafenib and dacarbazine in patients with advanced melanoma: a report from the 11715 Study Group. *J Clin Oncol*, **26**, 2178-85.
- Muszzbek N, Shah S, Carroll S, et al (2008). Economic evaluation of sorafenib in the treatment of hepatocellular carcinoma in Canada. *Curr Med Res Opin*, **24**, 3559-69.
- National Cancer Institute Common Toxicity Criteria (version 2 or 3) (2006). from [http://ctepcancer.gov/protocolDevelopment/electronic\\_application/ctc.htm](http://ctepcancer.gov/protocolDevelopment/electronic_application/ctc.htm)
- Paz-Ares LG, Biesma B, Heigener D, et al (2012). Phase III, randomized, double-blind, placebo-controlled trial of gemcitabine/cisplatin alone or with sorafenib for the first-line treatment of advanced, nonsquamous non-small-cell lung cancer. *J Clin Oncol*, **30**, 3084-92.
- Printz C (2009). Clinical trials of note. Sorafenib as adjuvant treatment in the prevention of disease recurrence in patients with hepatocellular carcinoma (HCC) (STORM). *Cancer*, **115**, 4646.
- Ranpura V, Hapani S, Wu S (2011). Treatment-related mortality with bevacizumab in cancer patients: a meta-analysis. *JAMA*, **305**, 487-94.
- Ratain MJ, Eisen T, Stadler WM, et al (2006). Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. *J Clin Oncol*, **24**, 2505-12.
- Rini BI, Escudier B, Tomczak P, et al (2011). Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet*, **378**, 1931-9.
- Scagliotti G, Novello S, von Pawel J, et al (2010). Phase III study of carboplatin and paclitaxel alone or with sorafenib in advanced non-small-cell lung cancer. *J Clin Oncol*, **28**, 1835-42.
- Schutz FA, Je Y, Richards CJ, Choueiri TK (2012). Meta-analysis of randomized controlled trials for the incidence and risk of treatment-related mortality in patients with cancer treated with vascular endothelial growth factor tyrosine kinase inhibitors. *J Clin Oncol*, **30**, 871-7.
- Shen BQ, Lee DY, Zioncheck TF (1999). Vascular endothelial growth factor governs endothelial nitric-oxide synthase expression via a KDR/Flk-1 receptor and a protein kinase C signaling pathway. *J Biol Chem*, **274**, 33057-63.
- Sivendran S, Liu Z, Portas LJ, Jr., et al (2012). Treatment-related mortality with vascular endothelial growth factor receptor tyrosine kinase inhibitor therapy in patients with advanced solid tumors: a meta-analysis. *Cancer Treat Rev*, **38**, 919-25.
- Sonpavde G, Bellmunt J, Schutz F, Choueiri TK (2012). The double edged sword of bleeding and clotting from VEGF inhibition in renal cancer patients. *Curr Oncol Rep*, **14**, 295-306.
- Spigel DR, Burris HA, Greco FA, et al (2011). Randomized, double-blind, placebo-controlled, phase II trial of sorafenib and erlotinib or erlotinib alone in previously treated advanced non-small-cell lung cancer. *J Clin Oncol*, **29**, 2582-9.
- Wang Y, Wang L, Liu Y, et al (2011). Randomize trial of cisplatin plus gemcitabine with either sorafenib or placebo as first-line therapy for non-small cell lung cancer. *Zhongguo Fei Ai Za Zhi*, **14**, 239-44.
- Wilhelm SM, Carter C, Tang L, et al (2004). BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. *Cancer Res*, **64**, 7099-109.
- Wu S, Chen JJ, Kudelka A, Lu J, Zhu X (2008). Incidence and risk of hypertension with sorafenib in patients with cancer: a systematic review and meta-analysis. *Lancet Oncol*, **9**, 117-23.
- Zachary I, Gliki G (2001). Signaling transduction mechanisms mediating biological actions of the vascular endothelial growth factor family. *Cardiovasc Res*, **49**, 568-81.