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Risk of fatal adverse events in cancer patients treated with sunitinib

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ABSTRACT

Sunitinib, a tyrosine kinase inhibitor, is widely used in several malignancies. However, the association between sunitinib administration and fatal adverse events (FAEs) is not completely clear. Here, to calculate the overall incidence and relative risks (RRs) of FAE induced by sunitinib, PubMed and Embase were searched from inception to September 2017 for phase III randomized controlled trials (RCTs). A total of 7470 patients with a variety of solid tumors from 12 trials were included in this study. The overall incidence of FAEs with sunitinib was 1.2% (95% CI: 0.7%–1.8%). Compared with control, the addition of sunitinib significantly increased the risk of FAEs (RR, 2.34; 95% CI, 1.34–4.09; $P < 0.001$). Trial sequential analysis demonstrated the cumulative z curve crossed the trial sequential monitoring boundary, established sufficient and conclusive evidence. Accordingly, further studies were unlikely to alter this conclusion. The association between sunitinib and FAEs varied significantly with treatment duration or treatment strategy, but not with tumor types or sunitinib dosage. The most common causes of FAEs was hemorrhage (26.9%). In conclusion, the use of sunitinib was associated with an increased risk of FAEs in patients with solid tumors.

1. Introduction

Sunitinib, one of the most common used agent targeting tyrosine kinase inhibitor (TKI), has been approved by the US Food and Drug Administration (FDA) for the treatment of gastrointestinal stromal tumor (GIST) (Demetri et al., 2006), renal-cell carcinoma (RCC) (Motzer et al., 2007), and pancreatic neuroendocrine tumor (PNT) (Raymond et al., 2011). It can inhibit the activity of vascular endothelial growth factor receptor (VEGFR-1,2 and 3); stem cell factor receptor (KIT); platelet-derived growth factor receptor (PDGFR-α and β); Fms-like TK-3 (FLT3); neurotrophic factor receptor; and colony-stimulating factor receptor type 1 (Hao and Sadek, 2016; Oudard et al., 2011). Some receptors, such as VEGFR, KIT and PDGFR, are expressed in many kinds of tumors (Hao and Sadek, 2016), implying that sunitinib may have the potential for use in other cancer treatments. Meanwhile, these receptors also play important roles in vascular function, physiological angiogenesis, cellular growth and division, and wound healing (Gyawali et al., 2017; Oudard et al., 2011; Ranpura et al., 2011). Accordingly, the administration of sunitinib can cause a variety of serious adverse effects including hemorrhage, arterial thrombosis, congestive heart failure, hypothyroidism, renal dysfunction, and wound dehiscence (Baggstrom et al., 2017; Barrios et al., 2010; Bergh et al., 2012; Carrato et al., 2013; Crown et al., 2013; Demetri et al., 2006; Haas et al., 2016; Michaelson et al., 2014; Motzer et al., 2007; Ravaud et al., 2016; Raymond et al., 2011; Scagliotti et al., 2012). Although fatal adverse events (FAEs) have occasionally been reported in subjects treated with sunitinib, no significant and definitive results have been established. In clinic, the incidence and risk of FAE induced by sunitinib treatment are frequently overlooked during the therapy decision-making process.

Here, to better understand the association between FAEs and sunitinib administration, we undertook a meta-analysis among patients with solid tumor in phase 3 randomized clinical trials (RCTs). Furthermore, we applied trial sequential analysis (TSA) to examine whether the currently available evidence was sufficient and conclusive.

2. Methods

The present study was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Liberati et al., 2009).

2.1. Literature search and study selection

A comprehensive systematic search of PubMed and Embase databases from January 1966 to September 2017 was conducted without

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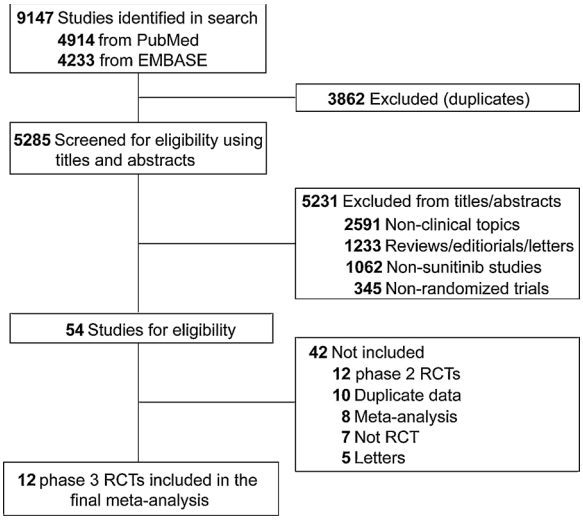

Fig. 1. Selection of trials included in the meta-analysis.

any language restrictions. Considering recent progress with sunitinib had not been published, systematic searches were also carried out in American Society of Clinical Oncology and European Society of Medical Oncology between January 2000 and September 2017. The search keywords and medical subject headings used were *Sunitinib, SUTENT* and *SU11248*. All investigators independently conducted the initial search, carefully screened the title and abstract for relevance, and identified trials as excluded, included and uncertain. For those uncertain studies, the full-texts were reviewed for the confirmation of eligibility. Any discrepancy was resolved by discussion.

In this study, both inclusion and exclusion criteria were pre-specified. To be eligible, trials had to meet the following criteria: (1) population: prospective phase 3 RCTs involving adult patients (> 18 years old) with solid tumor; (2) intervention: random assignment of patients to sorafenib or non-VEGF TKI control (placebo or chemotherapy) alone or in combination with other treatment; (3) outcomes: available information on FAEs or FAE rates and sample size. Other publications, including phase 1 and phase 2 trials, review articles, case report, preclinical papers, editorials, articles not dealing with sunitinib were excluded (Fig. 1). When multiple publications of the same study occurred, only the most recent and/or most complete reporting study was included.

The quality of trials was evaluated using the 7-item Jadad scale including randomization, double blinding, and withdrawals as previously described (Jadad et al., 1996).

2.2. Data extraction

The primary aim of this study was to establish the association between sunitinib administration and FAEs in cancer patients. FAE, defined by Common Terminology Criteria for Adverse Events 3.0 criteria in all the included trials, referred to death caused by sunitinib treatment.

Eligible abstracts were collected and full texts of relevant articles were reviewed for the trial design and reporting of FAEs. The following items were extracted: name of the first author, year of publication, masking method, tumor type, number of patients enrolled, number of patients for safety analysis, therapy strategy, median treatment duration, median follow-up, median overall survival, and number of FAEs (Table 1). All data were extracted independently by all reviewers, any discrepancies were resolved by discussion and consensus.

2.3. Trial sequential analysis

Random errors increase the risk of type I error (false-positive results) in meta-analysis because of sparse data and/or repetitive examining (Wetterslev et al., 2008). As a result, trial sequential analysis was introduced (Brok et al., 2008; Wetterslev et al., 2008). It can determine whether the data in one meta-analysis is reliable and conclusive. When the cumulative z curve crosses the trial sequential monitoring boundary or enters the futility area, a sufficient level of evidence for the anticipated intervention effect may have been reached and no further trials are needed. If the z curve crosses none of the boundaries and the required information size has not been reached, there is insufficient evidence to reach a conclusion. Here, we estimated the required information size using $\alpha = 0.05$ (two-sided), $\beta = 0.20$ (power of 80%). Trial sequential analysis was conducted by TSA version 0.9.5.9 Beta (http://www.ctu.dk/tsa).

2.4. Statistical analysis

The primary analysis examined the overall incidence, RR and corresponding 95% CI of FAEs in patients treated by sunitinib. To calculate the incidence, the number of patients receiving sunitinib and the number of FAEs were extracted from every trial. For the calculation of RR, patients assigned to sunitinib arm were compared with those assigned to control arm. When trials reported no FAE in one arm, we applied a classic half-integer continuity correction to calculate RR.

Statistical heterogeneity across trials was evaluated by Cochrane's Q statistic. The I^2 statistic was calculated to assess the extent of inconsistency contributable to the heterogeneity across different studies (Higgins et al., 2003). The assumption of homogeneity was considered invalid for $I^2 > 25\%$ or $p < 0.05$. Summary RRs and incidences were calculated using fixed-effects model or random-effects model depending on the heterogeneity. To check the impact of various clinicopathological variables on FAE, we further conducted post hoc subgroup analysis based on masking method, median treatment duration, tumor type, treatment strategy, and sunitinib dosage.

Potential publication bias was assessed by visual inspection of a funnel plot, and also evaluated using the tests of Egger et al. (Egger et al., 1997) and Begg et al. (Begg and Mazumdar, 1994). Two-sided $P < 0.05$ were considered statistically significant. All analysis was conducted by Stata 12.0 (StataCorp, USA).

3. Result

3.1. Search results

A total of 9147 potentially relevant articles were identified from the initial search, including 4914 studies from PubMed and 4233 trials from Embase. 3862 articles were excluded because of duplications. After screening of titles and abstracts, 5231 studies did not meet the inclusion criteria. Further reviewing the whole texts of the remaining 54 potentially eligible articles, 12 phase 3 RCTs were enrolled for the final analysis (Fig. 1) (Baggstrom et al., 2017; Barrios et al., 2010; Bergh et al., 2012; Carrato et al., 2013; Crown et al., 2013; Demetri et al., 2006; Haas et al., 2016; Michaelson et al., 2014; Motzer et al., 2007; Ravaud et al., 2016; Raymond et al., 2011; Scagliotti et al., 2012). Of these trials, 7 compared sunitinib versus placebo/control as single agents (Demetri et al., 2006; Baggstrom et al., 2017; Barrios et al., 2010; Haas et al., 2016; Motzer et al., 2007; Ravaud et al., 2016; Raymond et al., 2011) and 5 compared chemotherapy plus sorafenib versus chemotherapy plus placebo (Bergh et al., 2012; Carrato et al., 2013; Crown et al., 2013; Michaelson et al., 2014; Scagliotti et al., 2012).

Table 1
Characteristics of trials included in the meta-analysis.

Study	Masking method	Tumor type	No. of patients (enrolled)	No. of patients (safety)	Treatment	Median treatment duration (weeks, range)	Median follow-up (months, 95% CI)	Median OS (months, 95% CI)	FAE	Jadad score
Demetri, 2006	Double blind	GIST	207	202	Sunitinib 50 mg/d	8.0(0.1–33.7)	< 36.0	18.2(15.3–20.8)	0	5
			105	102	Placebo	4.2(0.3–24.0)		16.2(11.4–24.0)	0	
Scagliotti, 2012	Double blind	NSCLC	480	473	Sunitinib 37.5 mg/d + erilotinib 150 mg/d	12.0(4.0–120.0)	21.3	9.0(8.4–10.2)	4	5
			480	477	Placebo + erilotinib 150 mg/d	12.0(4.0–124.0)	22.0	8.5(7.4–9.8)	4	
Michaelson, 2014	Double blind	PC	584	584	Sunitinib 37.5 mg/d + prednisone 10 mg/d	14.0(0.1–111.9)	8.7	13.1(12.0–14.1)	12	5
			289	285	Placebo + prednisone 10 mg/d	13.9(0.9–94.4)		11.8(10.8–14.2)	1	
Crown, 2013	Open label	BC	221	217	Sunitinib 37.5 mg/d + capecitabine 2000 mg/m^2/d	16.3(12.4–18.9)	14.3(13.4–15.2)	16.4(13.6–18.4)	2	3
			221	215	Capecitabine 2500 mg/m^2/d	20.4(17.1–24.1)	NR	16.5(14.2–18.6)	1	
Bergh, 2012	Open label	BC	296	295	Sunitinib 37.5 mg/d + docetaxel 75 mg/m^2/d	26.0(23.0–29.0)	18.0(17.6–18.4)	24.8(21.5–33.1)	2	3
			297	293	Docetaxel 100 mg/m^2/d	18.0(16.0–19.0)	NR	25.5(22.8–27.8)	0	
Carrato, 2013	Double blind	CRC	386	384	Sunitinib 37.5 mg/d + FOLFIRI	NR	< 30.0	20.3(17.4–NA)	12	5
			382	379	Placebo + FOLFIRI	NR		19.8(18.7–NA)	4	
Raymond, 2011	Double blind	PNT	86	83	Sunitinib 37.5 mg/d	4.6(0.4–17.5)	67.4	38.6(25.6–56.4)	1	3
			85	82	Placebo	3.7(0.0–20.2)		29.1(16.4–36.8)	1	
Motzer, 2007	Open label	RCC	375	375	Sunitinib 50 mg/d	24.0(4.0–60.0)	< 48.0	28.7(25.0–35.7)	0	3
			375	360	Interferon alfa 9MU	16.0(4.0–52.0)		23.7(19.4–29.3)	0	
Barrios, 2010	Open label	BC	238	238	Sunitinib 37.5 mg/d	8.7(0.1–69.3)	< 24.0	15.3(12.0–24.7)	5	3
			244	240	Capecitabine 2500 mg/m^2/d	8.7(0.6–77.1)		16.9(14.5–26.0)	2	
Baggstrom, 2017	Double blind	NSCLC	106	99	Sunitinib 37.5 mg/d	NR	20.6(6.3–60.9)	11.7(9.9–14.0)	3	5
			104	99	Placebo	NR	NR	12.1(9.8–15.3)	2	
Ravaud, 2016	Double blind	RCC	309	306	Sunitinib 50 mg/d	49.6(0.4–59.6)	64.8(62.4–67.2)	NR	0	5
			306	304	Placebo	49.6(0.1–54.8)	64.8(63.6–67.2)	NR	0	
Haas, 2016	Double blind	RCC	647	625	Sunitinib 50 mg/d	48.0	69.6(58.8–82.8)	NR	3	4
			647	626	Placebo	54.0	NR	NR	0	

Abbreviation: BC, breast cancer; CRC, colorectal cancer; GIST, gastrointestinal stromal tumor; NSCLC, non-small-cell lung cancer; FAE, fatal adverse event; PC, prostate cancer; PNT, pancreatic neuroendocrine tumor; RCC, renal-cell carcinoma. FOLFIRI, irinotecan 180mg/m^2, levo-leucovorin 200mg/m^2 followed by fluorouracil 400mg/m^2; NR, not reported.

3.2. Study quality

Randomized treatment allocation sequences were generated in all trials. 8 trials were double blinded (Demetri et al., 2006; Michaelson et al., 2014; Raymond et al., 2011; Scagliotti et al., 2012; Carrato et al., 2013; Baggstrom et al., 2017; Ravaud et al., 2016; Haas et al., 2016), 4 studies were open labelled (Motzer et al., 2007; Crown et al., 2013; Bergh et al., 2012; Barrios et al., 2010). FAEs were reported in all trials. Follow-up time was adequate for each trial. We graded the quality of each study using the 7-item Jadad score that provides a score between 0 and 5 for each study. All studies included in this meta-analysis had a score of 3–5 indicating good quality (Table 1). The association of sunitinib with FAE did not show significant difference with Jadad scores (score < =4 vs score > 4; $P = 0.37$).

3.3. Patients

A total of 7470 patients were enrolled in the eligible 12 RCTs (Table 1). All the subjects in these trials had an Eastern Cooperative Oncology Group (ECOG) performance status between 0 and 2, and adequate hepatic, renal, cardiac and hematologic function. Safety population consisted of 7340 subjects (sunitinib, 3878; control, 3462). Underlying malignancies included RCC (3 trials) (Motzer et al., 2007; Ravaud et al., 2016; Haas et al., 2016), breast cancer (BC, 3 trials) (Crown et al., 2013; Bergh et al., 2012; Barrios et al., 2010), lung cancer (LC, 2 trials) (Scagliotti et al., 2012; Baggstrom et al., 2017), GIST (1 trial) (Demetri et al., 2006), prostate cancer (PC, 1 trial) (Michaelson et al., 2014), colorectal cancer (CRC, 1 trial) (Carrato et al., 2013), and PNT (1 trial) (Raymond et al., 2011).

3.4. Incidence of FAEs

There were 59 FAEs (sunitinib, 44; control, 15) among 7340 patients. The highest incidence (3.1%; 95% CI, 1.4%–4.9%) was observed in one colorectal cancer trial (Carrato et al., 2013), and the lowest incidences were observed in three RCTs in which no FAEs occurred (Demetri et al., 2006; Motzer et al., 2007; Ravaud et al., 2016). Using a random-effects model (heterogeneity test: Q = 15.89; $P = 0.04$; $I^2 = 49.6\%$), the summary incidence of FAEs in patients receiving sunitinib was 1.2% (95% CI, 0.7%–1.8%).

Furthermore, we explored the possible causes of the heterogeneity. As shown in Table 2, the incidence of FAEs varied significantly by tumor type ($P = 0.034$), treatment strategy ($P = 0.016$), and dosage ($P = 0.007$), suggesting these factors might contribute to the absolute risk of FAEs.

3.5. RR of FAEs

The summary RR of sunitinib-related FAE among the 7340 subjects from 12 RCTs was 2.34 (95% CI, 1.34–4.09; $P < 0.001$; Fig. 2), suggesting a significantly increased risk of FAEs associated with sunitinib compared with controls. No significant heterogeneity was identified ($Q = 4.77$; $I^2 = 0.0\%$; $P = 0.95$).

Because no FAE occurred in 3 studies (Demetri et al., 2006; Motzer et al., 2007; Ravaud et al., 2016), these trials were not qualified for trial sequential analysis (Fig. 3). TSA revealed that the cumulative z curve crossed both the conventional boundary for harm and the trial sequential monitoring boundary for harm, and entered the area of harm, which established sufficient and conclusive evidence. Thus, further trials were not needed and were unlikely to change our conclusions.

3.5.1. Risk of FAEs and masking method

Four included trials were open labelled (Motzer et al., 2007; Crown et al., 2013; Bergh et al., 2012; Barrios et al., 2010), which could introduce potential bias in the attribution of death. Further sensitivity analysis revealed that no statistically increased risk of FAEs associated with sunitinib in open labeled trials (RR, 2.49; 95% CI, 0.79–7.91; $P = 0.26$). However, risk of FAEs in placebo-controlled double-blinded trials showed significant alteration in the pooled effects (RR, 2.29; 95% CI, 1.21–4.34; $P = 0.003$).

3.5.2. Risk of FAEs and tumor type

We further examined RRs of FAEs with sunitinib based on tumor type. The highest RR were found in subjects with PC (RR, 5.89; 95% CI, 0.77–45.05; incidence, 2.1% vs 0.4%), and the lowest RR were observed in GIST (RR, 0.51; 95% CI, 0.01–25.27 incidence, 0.0% vs 0.0%). RRs of FAEs did not show statistical differences by tumor type ($P = 0.14$).

Table 2
Incidence and relative risk (RR) of FAE with sunitinib according to tumor type, median treatment duration, masking method, and dosage.

	No. of Trials	No. of FAEs/ No. of patients		Incidence of FAE, %(95% CI)		RR (95% CI)
		Sunitinib	Control	Sunitinib	Control	
Tumor type						
Renal-cell carcinoma	3	3/1306	0/1290	0.5(0.0–1.0)	0.0(0.0–0.0)	2.97(0.47–18.73)
Breast cancer	3	9/750	3/748	1.0(0.3–1.7)	0.6(0.0–1.3)	2.72(0.80–9.21)
Non-small-cell lung cancer	2	7/572	6/576	1.3(0.0–3.0)	0.9(0.1–1.7)	1.17(0.40–3.46)
Gastrointestinal stromal tumor	1	0/202	0/102	0.0(0.0–0.0)	0.0(0.0–0.0)	0.51(0.01–25.27)
Prostate cancer	1	12/581	1/285	2.1(0.9–3.2)	0.4(0.0–1.0)	5.89(0.77–45.05)
Colorectal cancer	1	12/384	4/379	3.1(1.4–4.9)	1.1(0.0–2.1)	2.96(0.96–9.10)
Pancreatic neuroendocrine tumor	1	1/83	1/82	1.2(0.0–3.6)	1.2(0.0–3.6)	0.99(0.06–15.53)
Treatment strategy						
Monotherapy	7	12/1928	5/1813	0.6(0.1–1.3)	0.3(0.0–0.8)	1.93(0.79–4.72)
Combination therapy	5	32/1950	10/1649	1.6(0.7–2.5)	0.6(0.0–1.2)	2.61(1.27–5.34)
Dosage						
37.5 mg/day	8	41/2370	15/2070	1.4(0.8–2.0)	0.5(0.2–0.8)	2.35(1.30–4.28)
50.0 mg/day	4	3/1508	0/1392	0.2(0.0–0.5)	0.0(0.0–0.0)	1.99(0.40–9.98)
Median treatment duration						
< = 12 weeks	4	10/996	7/901	0.7(0.1–1.4)	0.8(0.2–1.4)	1.36(0.54–3.42)
> 12 weeks	6	19/2399	2/2083	0.5(0.1–0.9)	0.1(0.0–0.3)	3.87(1.28–11.69)
Masking method						
Double blind	8	35/2753	12/2354	1.4(0.6–2.3)	0.7(0.3–1.2)	2.29(1.21–4.34)
Open label	4	9/1125	3/1108	1.0(0.3–1.7)	0.6(0.0–1.3)	2.49(0.79–7.91)
Overall	12	44/3878	15/3462	1.2(0.7–1.8)	0.4(0.1–0.6)	2.34(1.34–4.09)

Abbreviation: CI, confidence interval; FAE, fatal adverse event.

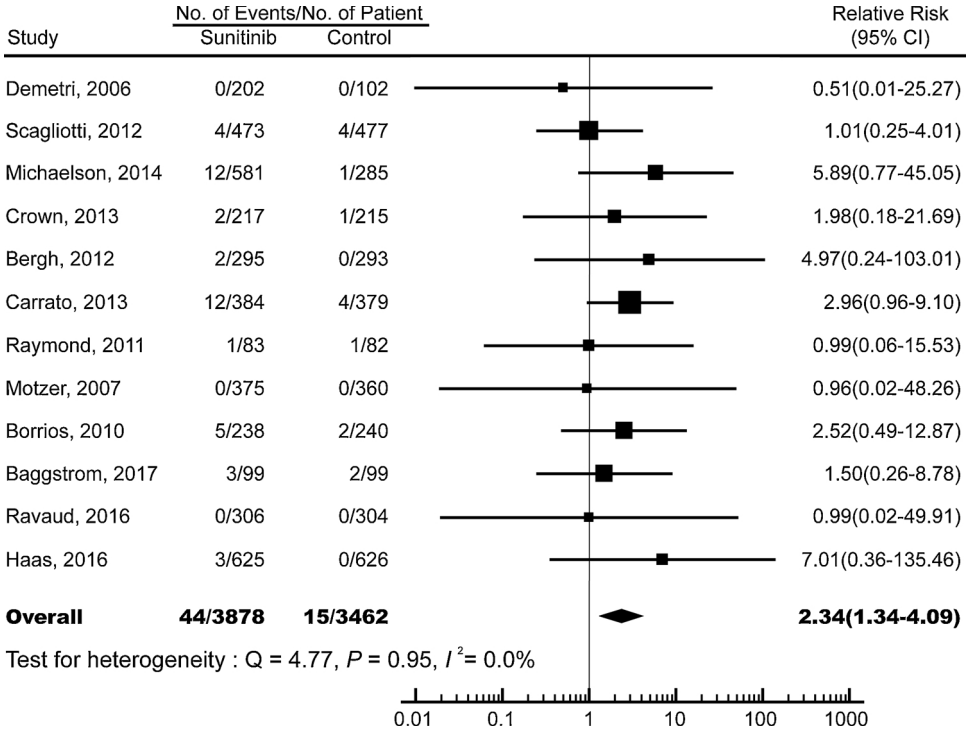

Fig. 2. Relative risk (RR) of fatal adverse events (FAEs) associated with sunitinib versus control.

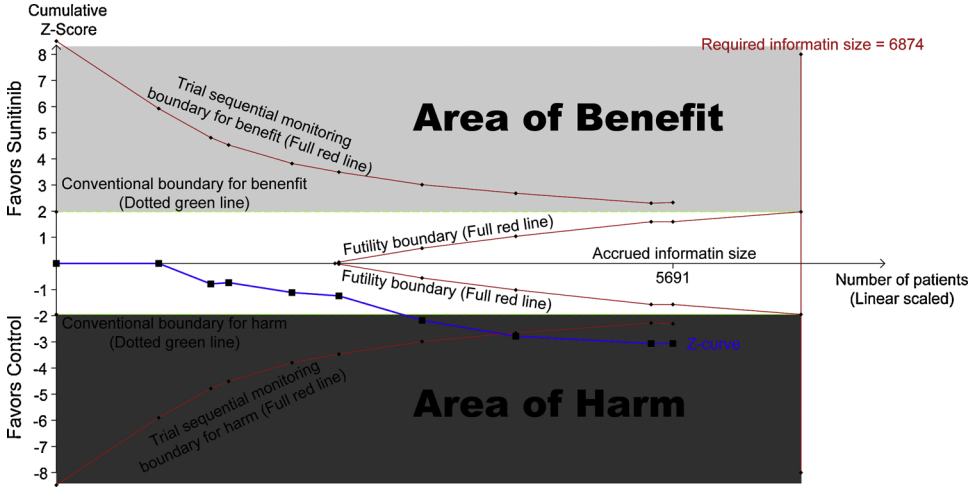

Fig. 3. Trial sequential analysis (TSA) of 9 RCTs comparing sunitinib with control (scaled trial distance). TSA of 9 trials (black filled squares) demonstrating that the cumulative *z* curve crossed both the conventional boundary for harm and the trial sequential monitoring boundary for harm, establishing conclusive and sufficient evidence and suggesting no further trials are needed. A diversity-adjusted required information size of 6874 patients was calculated using $\alpha = 0.05$ (two-sided) and $\beta = 0.20$ (power of 80%), an anticipated relative risk reduction of 20% in the control arm. X axis, number of patients randomized; Y axis, cumulative z score; horizontal green dotted lines, conventional boundaries (z score, ± 1.96; two-sided $p = 0.05$); Sloping red lines with black filled circles, trial sequential monitoring boundaries; blue line with black filled squares, *z* curve; vertical red line, required information size; upper light-gray rectangle, area of benefit; lower dark-grey rectangle, area of harm; middle white rectangle, futility area (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

3.5.3. Risk of FAEs and treatment strategy

To investigate whether chemotherapeutic agents could alter the association between risk of FAE and sunitinib, we conducted a subgroup analysis stratified according to treatment strategy. The RR of FAEs for combination therapy was 2.61 (95% CI, 1.27–5.34; $P < 0.001$; incidence, 1.6% vs 0.6%) vs 1.93 (95% CI, 0.79–4.72; $P = 0.21$; incidence, 0.6% vs 0.3%) for sunitinib monotherapy. This difference in RRs between monotherapy and combination therapy was statistically significant ($P = 0.04$).

3.5.4. Risk of FAEs and sunitinib dosage

From 8 RCTs, sunitinib at 37.5 mg/day was associated with significant increase risk of FAEs, with an RR of 2.35 (95% CI, 1.30–4.28; $P = 0.02$; incidence, 1.4% vs 0.5%). Interestingly, sunitinib at 50 mg/day was not associated with an increased risk of FAEs (RR, 1.99; 95% CI, 0.40–9.98; $P = 0.63$; incidence, 0.2% vs 0.0%). This might be due to the lack of statistical power and further studies were needed. Overall, no statistical difference was observed between high and low dose of sunitinib in terms of FAEs ($P = 0.31$).

3.5.5. Risk of FAEs and sunitinib treatment duration

We also conducted a subgroup analysis stratified by median treatment duration. Median treatment duration over 12 weeks was associated with significant increase risk of FAEs, with an RR of 3.87 (95% CI, 1.28–11.69; $P < 0.001$; incidence, 0.5% vs 0.1%). In contrast, median treatment duration less than 12 weeks was not associated with an increased risk of FAEs (RR, 1.36; 95% CI, 0.54–3.42; $P = 0.81$; incidence, 0.7% vs 0.8%). The difference was statistically significant ($P = 0.04$).

3.5.6. Risk of specific FAEs

Among the total 44 FAEs with sunitinib treatment, 26 (59.1%) had

Table 3
Incidence and relative risk of specific FAEs with sunitinib.

FAEs	No. of Trials	No. of FAEs/ No. of patients		Incidence of FAE, %(95% CI)		RR (95% CI)
		Sunitinib	Control	Sunitinib	Control	
Specified	8	26/2414	13/2411	0.9(0.3–1.5)	0.8(0.3–1.2)	1.89(1.01–3.56)
Unspecified	6	18/2049	2/1748	0.6(0.1–1.0)	0.3(0.0–0.7)	3.65(1.20–11.14)
Hemorrhage	5	7/1819	4/1821	0.3(0.0–0.5)	0.1(0.0–0.2)	1.60(0.53–4.89)
Cardiac	4	4/1000	0/994	0.3(0.0–0.7)	0.0(0.0–0.0)	2.98(0.60–14.73)
Brain and neural system	3	3/1336	2/1343	0.2(0.0–0.4)	0.1(0.0–0.3)	1.41(0.28–7.13)
Gastro–intestine	3	2/1226	1/1220	0.2(0.0–0.2)	0.1(0.0–0.1)	1.39(0.28–7.03)
Overall	12	44/3878	15/3462	1.2(0.7–1.8)	0.4(0.1–0.6)	2.34(1.34–4.09)

Abbreviation: CI, confidence interval; FAE, fatal adverse event.

specified adverse events, while the rest FAEs (n = 18, 40.9%) had unspecified causes (Table 3). Hemorrhage was the most frequently occurring FAE which reported in five studies and represented a total of 7 death or 26.9% of all specified FAEs. Other common reported death occurred in heart (n = 4, 15.4%), and brain and neural system (n = 3, 11.5%).

3.6. Publication bias

There was no evidence of publication bias by inspection of the funnel plot and formal statistical tests (Begg's test, $P = 0.64$; Egger's test, $P = 0.57$).

4. Discussion

To our knowledge, this is the first meta-analysis focused specially on the incidence and risk of sunitinib-related FAEs. Based on 12 phase 3 RCTs, our study reveals that the administration of sunitinib is associated with a significant increased risk of FAEs with an RR of 2.34 (incidence, 1.2% vs 0.4%) in patients with solid tumor. In addition, TSA confirms that our result is solid and reliable, further studies are unlikely to alter this conclusion. Since sunitinib is commonly used in tumor therapy, it is important that both clinicians and patients recognize this risk of sunitinib-related mortality.

Meta-analysis is a powerful tool for investigating rare events like FAE given it can comprehensively synthesize data from various trials to achieve a robust and reliable result. Previously, two independent studies demonstrated that there were no association between sunitinib treatment and risk of FAEs in cancer patients (Schutz et al., 2012; Sivendran et al., 2012). In one meta-analysis of VEGFR-TKIs, 3 trials with 1388 patients (sunitinib, 699; control, 689) were included in the sunitinib subgroup analysis. The incidence of FAEs was 1.5%, close to our estimate of 1.2% in the present study. However, the RR was 1.39 (95% CI, 0.41–4.67; $P = 0.59$) (Schutz et al., 2012). In another meta-analysis of VEGFR-TKIs, 5 trials with 1770 subjects (sunitinib, 942; control, 828) were included in the sunitinib subgroup analysis. The incidence of FAEs was 0.70%, and the RR was 1.09 (95% CI, 0.47–2.51; $P = 0.84$) (Sivendran et al., 2012). Here, the primary finding of our meta-analysis was not consistent with these previous ones. It should be noted that there were several differences between our study and others. First, these preivous studies included no more than 5 trils and 1770 subjects. In comparison, our study included 12 well-conducted, high quality, phase 3 RCTs with over 7000 adult patients with solid tumors. Additionally, the lack of hetetogenity in the RR of FAEs suggested a well selection of the eligible trials. With increased statistical power of more than 5000 cases, our study was most up-to-date and most comprehensive one, which should be more solid and reliable. Second, to further increase the robustness of our data, we applied TSA to evaluate the impact of random error and repetitive testing. The results showed that our meta-analysis established conclusive, sufficient evidence. Third, we explored the relationship between various clinicopathological characteristics and sunitinib-related FAEs.

The development of VEGFR-TKIs has a dramatic effect on the outlook of cancer treatment over the last decade. There have been several meta-analyses estimating FAEs with VEGFR inhibitors (Gyawali et al., 2017; Ranpura et al., 2011; Schutz et al., 2012; Sivendran et al., 2012). Currently, it is generally accepted that the use of VEGFR TKI is associated with an increased risk of FAEs compared with control. However, the incidence and relative risk vary among different agents. Previous study showed that the addition of bevacizumab was associated with an increased risk of FAEs (RR, 1.33; 95% CI, 1.02–1.73) compared with control (Ranpura et al., 2011). Sorafenib, another agent antagonizes the intracellular domain of the VEGFR and blocks the downstream signaling, also could significantly increase the risk of FAEs (RR, 1.82; 95% CI, 1.05–3.14) (Gyawali et al., 2017). Interestingly, although all these three drugs had similar toxicity class-effect profiles, sunitinib seemed to be deadlier than bevacizumab and sorafenib were. These discrepancies might be partly due to the differences in the mechanisms of action among these agents, the type of tumor, dosage, and various treatment duration.

We assessed the associations of sunitinib administration with FAEs based on tumor type, treatment strategy, sunitinib dose, median treatment duration, and masking method. The incidences of FAEs varied significantly among different types of tumors, reflecting the association of underlying tumor biology and sunitinib treatment. However, our analysis demonstrated the risk of FAEs did not vary significantly with tumor types. Further studies are needed to study these associations. Notably, our data revealed the association between sunitinib and FAEs depended on whether chemotherapeutic agents were administrated. This result might reflect an interaction between sunitinib and certain chemotherapeutic agents in causing severe toxic effects. The association of sunitinib with FAEs was statistically significant among studies with longer treatment duration but was not different among studies with shorter treatment duration. Our results suggested a treatment duration dependency in the association between sunitinib and FAEs.

Our study has several important clinical and research implications. Generally speaking, targeted cancer therapy is a two-edged sword. However, clinicians and patients often overestimate the beneficial side and overlook the harmful side (Hoffmann and Del Mar, 2015). It is reported that adverse drug reactions account for 4.6% of all hospital fatalities (Lazarou et al., 1998). Accordingly, careful review of potential adverse events should play an essential role in the decision-making process. Our result here should be important in considering the risk/benefit trade-off of sunitinib therapy by providing the overall incidence and relative risk of FAEs.

In order to reduce the toxicity burden, clinicians should recognize that the nature of clinicopathological characteristics in patients can lead to differences in efficacy and tolerability of sunitinib. In the expanded access programs based in Korea and Japan, ethnicity was show to contribute to the incidence and severity of AE (Akaza et al., 2015; Hong et al., 2009). Although radiotherapy in associated with sunitinib seemed safe, Belgioia et al. implied that age might impact the safety and

efficacy of sunitinib, and suggested the specific clinical trials in elderly patients should be taken (Belgioia et al., 2019). Additionally, the heterogeneity in toxicity can be explained partially through genomic variability, such as single nucleotide polymorphisms. It was reported the VEGFR2 1191 T allele, one or two copies of TT in the ABCG2 haplotype were associated with the development of any toxicity higher than grade 2 (Erdem et al., 2012). Even so, there still remains a lack of information in terms of predictive markers and diagnostic strategy. The benefit/risk balance could be greatly improved by the identification of new predictive markers. Interestingly, it was proposed that AEs themselves might be the surrogate biomarkers of clinical efficacy (Kollmannsberger, 2016).

In clinical practice, proactive management starts even before a patient begin his/her treatment with sunitinib, such as the education on patients and their families, pre-treatment risk/benefit evaluation, and patients' counseling. Professionals in healthcare should be familiar with the administration of sunitinib to monitor patients effectively. Active management of sunitinib-related toxicities includes routine examination of clinical symptoms, laboratory variables, as well as early intervention. Proactive and effective treatment of AEs is important to maintain sunitinib treatment. Hence, low-grade toxicities should not be overlooked because sunitinib is taken on a daily basis. The potential impact of accumulating low-grade AEs on patients should be valued against the clinical performance constantly. Maximizing drug exposure was critical because it was related with longer overall survival and progression-free survival(Guida et al., 2014; Zhang et al., 2018). Moreover, our data revealed that dosage was an independent factor in sunitinib-related FAEs. Accordingly, any dose adjustment should be careful considered. In many cases, personalizing the treatment strategy can minimize toxicities (e.g. from 4-week-on/2-week-off to 2-week-on/1-week-off)(Guida et al., 2014).

Our study is restricted by several limitation. First, we could not fully characterize the reason of FAE, over 40% of death did not have any specified cause in sunitinib treatment arm. Identification of the exact reason of these FAEs could be helpful in developing the strategy for treating sunitinib-related motilities. Second, the eligible trials were carried out at different medical center by various researchers, and might have potential bias in reporting FAEs. Especially the attribution of FAE to sunitinib treatment was determined by investigators, who were associated with some subjectivity. Accordingly, the exact reason of FAE might not be fully studied even at single-patient level. However, by using meta-analysis to calculate the combined data, such potential bias could be avoided as much as possible. Third, some eligible trials were open labeled RCTs. Even for those double blinded studies, skillful doctors might identify sunitinib induced AE, which could lead to potential bias. Forth, the incidences of FAE among the eligible trials had significant heterogeneity. We adjusted this heterogeneity by conducting a random-effects model to achieve the overall incidence of FAEs. Even so, it might underestimate the real event rate given that trials without any death received disproportional weight in calculation.

In summary, addition of sunitinib significantly increases the risk of fatal adverse events. The risk/benefit should be properly weighted by both practitioners and patients in any treatment. Furthermore, clinician should provide rigorous monitoring to improve the outcomes.

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