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ORIGINAL RESEARCH

Increased risk of severe infections in cancer patients treated with vascular endothelial growth factor receptor tyrosine kinase inhibitors: a meta-analysis

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Background: Vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKIs) have been widely used in a variety of solid malignancies. Concerns have arisen regarding the risk of severe infections (≥grade 3) with use of these drugs, but the contribution of VEGFR-TKIs to infections is still unknown.

Methods: The databases of PubMed and abstracts presented at oncology conferences' proceedings were searched for relevant studies from January 2000 to December 2014. Summary incidences, Peto odds ratio (Peto OR), and 95% confidence intervals (CIs) were calculated by using either random-effects or fixed-effects models according to the heterogeneity of included studies.

Results: A total of 16,488 patients from 27 randomized controlled trials were included. The risk of developing severe (Peto OR 1.69, 95% CI: 1.45–1.96, $P<0.001$) and fatal infections (Peto OR 1.78, 95% CI: 1.13–2.81, $P=0.013$) was significantly increased in patients treated with VEGFR-TKIs when compared to controls. Exploratory subgroup analysis showed no effect of tumor types, phase of trials, or agent used on the Peto OR of severe infections. When stratified according to specific infectious events, the risks of high-grade febrile neutropenia, pneumonia, fever, and sepsis were increased compared with controls, with Peto ORs of 1.57 (95% CI: 1.30–1.88, $P<0.001$), 1.79 (95% CI: 1.29–2.49, $P<0.001$), 5.35 (95% CI: 1.47–19.51, $P=0.011$), and 3.68 (95% CI: 1.51–8.99, $P=0.004$), respectively. Additionally, VEGFR-TKIs significantly increased the risk of fatal sepsis (OR 3.66, 95% CI: 1.47–9.13, $P=0.005$) but not fatal pneumonia (OR 1.34, 95% CI: 0.80–2.25, $P=0.26$).

Conclusion: The use of VEGFR-TKIs significantly increases the risk of developing severe and fatal infectious events in cancer patients. A close monitoring for any signs of infections is recommended for patients treated with VEGFR-TKIs.

Keywords: VEGFR-TKIs, infections, cancer, randomized controlled trials, meta-analysis

Introduction

Tumor angiogenesis is a complex process that is crucial for tumor growth, invasion, and metastasis.[1–3] During the past decades, many new agents targeting vascular endothelial growth factor (VEGF) and its receptors (VEGFRs) have proven to be a successful strategy in patients with cancer. Until now, the US Food and Drug Administration has approved a number of VEGFR tyrosine kinase inhibitors (TKIs) in multiple indications: sunitinib, sorafenib, pazopanib, and axitinib have been approved for patients with metastatic renal cell carcinoma (RCC).[4–8] Moreover, sunitinib has been approved for pancreatic neuroendocrine tumors[9] and refractory gastrointestinal stromal tumors

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(GISTs),[10] and sorafenib has been approved for advanced hepatocellular carcinoma (HCC)[11] and radioiodine-refractory differentiated thyroid carcinoma.[12] Additionally, vandetanib has been approved for symptomatic or progressive medullary thyroid cancer,[13] and regorafenib has been approved for refractory advanced colorectal cancer[14] and GISTs.[15]

However, the toxicity profiles of VEGFR-TKIs are unique compared with the adverse effects typically associated with traditional cytotoxic anticancer therapies. They include mucocutaneous adverse events,[16–19] liver dysfunction,[20–23] gastrointestinal perforation,[24,25] and cardiovascular toxicities.[26–33] Additionally, severe infections (≥grade 3) associated with VEGFR-TKIs have been reported in randomized controlled trials (RCTs). However, the incidence has varied substantially among clinical trials, and there has been no systematic attempt to synthesize the data in order to define the overall incidence and risk of infections associated with these drugs. Therefore, we conducted a systematic review and meta-analysis of RCTs to determine the overall risk of developing severe infection in cancer patients treated with these drugs.

Methods

Data sources

Studies were identified by searching the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed (up to December 2014), Web of Science, and EMBASE, including abstracts from the leading conference proceedings. The search was limited to prospective RCTs published in English. Keywords were sorafenib, nexavar, BAY43-9006, sunitinib, sutent, SU11248, pazopanib, votrient, GW786034, vandetanib, caprelsa, ZD6474, axitinib, AG-013736, cediranib, AZD2171, tivozanib, regorafenib, BAY 73-4506, cabozantinib, brivanib, ramucirumab, IMC-1121B, nintedanib, BIBF 1120, motesanib, randomized controlled trials, and cancer. The search strategy also used text terms such as angiogenesis inhibitors and vascular endothelial growth factor receptor-tyrosine kinase inhibitors to identify relevant information (Supplementary material). When more than one publication or presentation was identified from the same clinical trial, the most recent report with complete information about infectious events was included for analysis. The quality of reports of clinical trials was assessed and calculated using the five-item Jadad scale including randomization, double-blinding, and withdrawals.[34]

Study selection

The purpose of this study was to determine whether VEGFR-TKIs contribute to the development of severe and fatal infectious events in patients with cancer. Therefore, we only selected those randomized clinical trials that directly compared patients with cancer treated with and without VEGFR-TKIs for analysis. Clinical trials that met the following criteria were included: (1) prospective randomized controlled Phase II and III trials in cancer patients, (2) randomized assignment of patients to VEGFR-TKIs treatment or control in addition to current chemotherapy and/or biological agent, and (3) events or event rate and sample size available for high-grade (grade 3–4) and fatal (grade 5) infectious events. Phase I trials were excluded because of interstudy variability in drug dosing as well as the small number of patients in these trials. Study selection was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[35]

Data extraction and clinical endpoints

Two investigators independently performed data extraction. Agreement between the two data extractors was assessed with the Kappa statistic test. The following information was recorded for each study: first author's name, year of publication, trial phase, number of patients enrolled, treatment arms, number of patients in treatment and controlled groups, underlying malignancy, median age, median progression-free survival and overall survival, adverse outcomes of interest (infectious events), and name and dosage of VEGFR-TKIs. The following adverse outcomes were considered as infectious events and were included in the analyses: infections (not specified), febrile neutropenia, sepsis, septic shock, fever, bacterial peritonitis, and pneumonia. Adverse events of severe infections (≥grade 3), as assessed and recorded according to the National Cancer Institute's common terminology criteria (version 2 or 3; http://ctep.cancer.gov), were extracted for analysis, which has been widely used in cancer clinical trials.

Statistical analysis

The principal summary measures were incidence, Peto odds ratio (Peto OR), and corresponding 95% confidence intervals (CIs). For the calculation of incidence, the number of patients experiencing infections and total number of patients treated with VEGFR-TKIs were extracted from the safety profiles of all selected clinical trials; the proportion of patients with infections and 95% CIs were derived for each study.

We also calculated the Peto ORs and 95% CIs of infections in patients assigned to VEGFR-TKIs vs control treatment. For one study that reported zero events in the treatment or control arm, we applied the classic half-integer correction

to calculate the relative risk (RR) and variance.[36] We also conducted the following prespecified subgroup analyses to find the potential risk factor of infections: tumor types, VEGFR-TKIs, and phase of trials. For each meta-analysis, the Cochran Q statistic and I^2 score were first calculated to determine heterogeneity among the proportions of the included trials.[37] For $P<0.10$ values of the Cochran Q statistic, the assumption of homogeneity was deemed invalid, and a random-effects model was reported. Otherwise, results from the fixed-effects model were reported. Additionally, we also calculated the number needed to harm from the absolute difference of the pooled estimates between the two groups. Finally, potential publication biases were evaluated with funnel plots for severe infections, which assessed the relative symmetry of individual study estimates around the overall estimate, followed by Begg's and Egger's tests. A two-tailed P-value of <0.05 without adjustment for multiplicity was considered statistically significant. The leave-one-out procedure was also performed for primary endpoint analysis. A two-tailed P-value of <0.05 was considered statistically significant. The results of the meta-analysis were reported as classic forest plots. All statistical analyses were performed by using Version 2 of the Comprehensive MetaAnalysis program (Biostat, Englewood, NJ, USA) and Open Meta-Analyst software version 4.16.12 (Tufts University).

Trial sequential analysis

Trial sequential analyses (TSAs) were performed post hoc to assess the risk of random errors and false-positive results, and to help clarify the need for additional trials. RR was used as effect estimate in a DerSimonian and Laid random-effects model. Zero-event trials were handled by adding 0.5 events to the two arms. We used two-sided tests, type I error set at 5% and power set at 80%. In the TSA based on all trials, the boundaries were calculated with a relative risk reduction set at an arbitrary level of 60% and with model variance-based heterogeneity correction. The incidence of severe infections in the control group was set at 3.3% for cancer patients. TSA was performed in TSA V.0.9 β (http://www.ctu.dk/tsa/).

Results

Search results

Our search yielded 982 clinical studies relevant to VEGFR-TKIs (sunitinib, sorafenib, pazopanib, vandetanib, axitinib, cediranib, tivozanib, regorafenib, cabozantinib, nintedanib, brivanib, ramucirumab, and motesanib). After excluding review articles, Phase I studies, single-arm Phase II studies, case reports, meta-analyses, observation studies, duplicated RCTs, commentaries, letters, and RCTs without adequate infections data (Figure 1), we selected 27 RCTs, including 24 Phase III and three Phase II trials, for the purpose of analysis (Table 1). A total of 16,488 patients from 27 clinical trials were included for analysis. The characteristics of patients and studies are listed in Table 2. Underlying malignancies included non-small-cell lung cancer (NSCLC) (ten trials),[38–47] colorectal cancer (three trials),[14,48,49] thyroid cancer (three trials),[50–52] HCC (two trials),[53,54] advanced breast cancer (one trial),[55] urothelial cancer

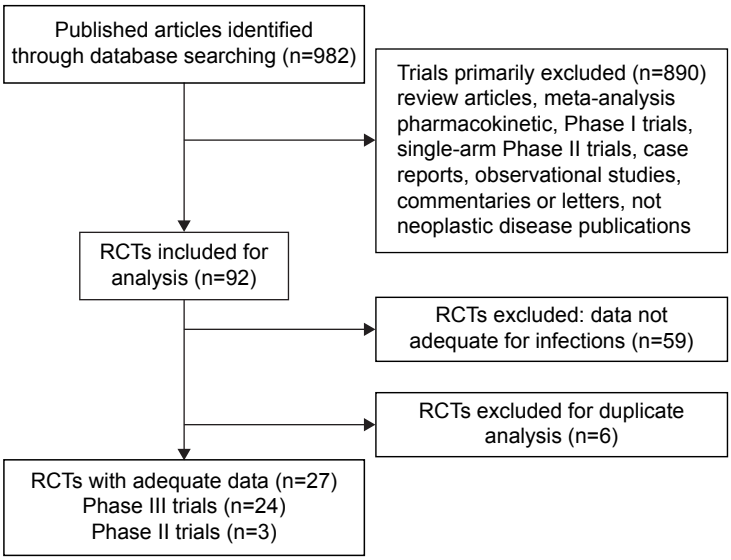

Figure 1 Selection process for prospective randomized controlled trials included in the meta-analysis.
Abbreviation: RCT, randomized controlled trial.

Table 1 Relative risk of severe infectious events according to tumor types, VEGFR-TKIs, and phases of trials

Groups	Studies, n	Severe infectious events, n/total, n		RR (95% CI)	*P*-value	Numbers needed to harm	*P*-value for group difference
		VEGFR-TKIs	Control				
Tumor types							
NSCLC	10	362/4,891	210/4,597	1.65 (1.39–1.96)	<0.001	35	0.85
CRC	3	43/1,389	19/995	1.99 (1.19–3.33)	0.009	84	
Thyroid cancer	3	6/510	1/381	3.57 (0.78–16.33)	0.10	109	
HCC	2	2/293	4/302	0.52 (0.10–2.65)	0.44	155	
Others	9	71/1,854	40/1,492	1.73 (1.17–2.56)	0.006	87	
VEGFR-TKIs							
Vandetanib	7	111/2,387	69/1,936	1.25 (0.92–1.70)	0.16	92	0.48
Sorafenib	7	87/1,467	43/1,497	2.11 (1.48–3.00)	<0.001	33	
Sunitinib	5	52/1,732	23/1,435	2.18 (1.35–3.53)	0.001	72	
Cediranib	2	14/653	8/511	1.56 (0.66–3.65)	0.31	174	
Regorafenib	2	9/637	2/319	1.99 (0.57–7.02)	0.28	128	
Others	4	211/2,061	129/2,069	1.62 (1.32–2.00)	<0.001	25	
Phases of trials							
Phase II	4	22/680	15/424	1.21 (0.60–2.44)	0.60	336	0.29
Phase III	23	462/8,257	259/7,343	1.71 (1.47–1.99)	<0.001	48	
Overall	27	484/8,937	274/7,767	1.69 (1.45–1.96)	<0.001	53	NA

Abbreviations: VEGFR-TKIs, vascular endothelial growth factor receptor tyrosine kinase inhibitors; RR, relative risk; CI, confidence interval; NSCLC, non-small-cell lung cancer; CRC, colorectal cancer; HCC, hepatocellular carcinoma; NA, not available.

(one trial),[56] pancreatic cancer (one trial),[57] gastric cancer (one trial),[58] melanoma (one trial),[59] RCC (one trial),[60] acute myeloid leukemia (one trial),[61] castration-resistant prostate cancer (one trial),[62] and GIST (one trial).[15] When examining by agent, sorafenib was investigated in seven trials (2,964 patients), vandetanib in seven trials (4,223 patients), sunitinib in five trials (3,167 patients), cediranib in two trials (1,164 patients), regorafenib in two trials (956 patients), motesanib in one trial (1,072 patients), ramucirumab in one trial (1,253 patients), nintedanib in one trial (655 patients), and brivanib in one trial (502 patients). The Cohen–Kappa statistic for agreement between the two reviewers was 0.866 (95% CI: 0.80–0.93).

Trial quality

Randomized treatment allocation sequences were generated in all trials. Twenty-one trials were placebo-controlled and double-blinded. Follow-up time was generally adequate for each trial and included a period of approximately 2–4 weeks after end of therapy on trial. All the trials were of moderately high to high quality (Jadad score 3–5).

RR of severe and fatal infections

Severe infections occurred in 484 out of 8,937 (3.8%) patients receiving VEGFR-TKIs. In the non-TKI group, severe infections occurred in 274 out of 7,767 (3.0%) patients. Subjects in the VEGFR-TKI group were at significantly higher risk of severe infections than subjects in the non-TKI group (OR 1.69, 95% CI: 1.45–1.96, $P<0.001$; Figure 2). There was no evidence of heterogeneity ($Q=31.61$, $P=0.206$, $I^2=17.76\%$). Fatal infections occurred in 52 out of 4,923 (1.0%) patients receiving VEGFR-TKIs. In the non-TKI group, fatal infections occurred in 26 out of 4,111 (0.8%) patients. There was significant difference in risk of fatal infections between subjects in the VEGFR-TKI group and those in the non-TKI group (OR 1.78, 95% CI: 1.13–2.81, $P=0.013$; Figure 3), and there was no evidence of significant heterogeneity ($Q=15.0$, $P=0.31$, $I^2=13.4\%$). We also did sensitivity analysis to examine the stability and reliability of pooled severe ORs by sequential omission of individual studies. The results indicated that the significance estimate of pooled severe RRs was not significantly influenced by omitting any single study (Figure 4).

Subgroup analysis of RR of severe infections

To determine whether the observed increase in ORs of developing severe infections was the result of confounding bias, we performed subgroup analyses according to the underlying malignancy, VEGFR-TKIs, and phase of trials. When stratified by tumor types, a significantly increased risk of severe infections was observed in colorectal cancer (OR 1.99, 95% CI: 1.19–3.33, $P=0.009$) and NSCLC (OR 1.65, 95% CI: 1.39–1.96, $P<0.001$), while the risk of severe infections was decreased in HCC (OR 0.52, 95% CI: 0.10–2.65, $P=0.44$; Table 1). However, no significant differences in ORs of severe infections were found

Table 2 Baseline characteristics of 27 randomized controlled trials in the meta-analysis (n=1,488)

Authors (year)	Histology	Phase	Patients enrolled	Treatment arm	Median age (years)	Median PFS (months)	Median OS (months)	Number for analysis	Severe infections	Reported infectious events
Natale et al (2009)[47]	NSCLC	III	168	Vandetanib 300 mg	61	2.6	6.1	83	3	Pneumonia, sepsis
				Gefitinib	63	1.9	7.4	85	0	
Herbst et al (2010)[46]	NSCLC	III	1,391	Vandetanib 100 mg qd po + Doc	59	4	10.3	689	46	Febrile neutropenia
				Placebo + Doc	59	3.2	9.9	690	38	
Barrios et al (2010)[55]	ABC	III	482	Sunitinib 37.5 mg qd po	53	2.8	15.3	238	1	Septic shock
				Capecitabine	53	4.2	24.6	240	0	
Scagliotti et al (2010)[45]	NSCLC	III	926	Sorafenib 400 mg bid po + PTX + CBP	62	4.6	10.7	436	38	Febrile neutropenia, pneumonia, infections
				Placebo + PTX + CBP	63	54	10.6	459	12	
Abou-Alfa et al (2010)[54]	HCC	II	96	Doxorubicin + sorafenib 400 mg bid po qd	66	6	13.7	47	0	Febrile neutropenia
				Doxorubicin + placebo	65	2.7	6.5	49	4	
Natale et al (2011)[44]	NSCLC	III	1,240	Vandetanib 300 mg qd po	61	2.6	6.8	623	9	Pneumonia
				Erlotinib	61	2	7.7	614	5	
Leboulleux et al (2012)[52]	Thyroid cancer	II	145	Vandetanib 300 mg qd po	63	11.1	NR	72	1	Pneumonia
				Placebo	64	5.9	NR	73	1	
Lee et al (2012)[43]	NSCLC	III	924	Vandetanib 300 mg qd po	60	1.9	8.5	619	47	Infections, pneumonia
				Placebo	60	1.8	7.8	303	21	
Wells et al (2012)[51]	Thyroid cancer	III	331	Vandetanib 300 mg qd po	50.7	30.5	NR	231	2	Aspiration, pneumonia, staphylococcal sepsis
				Placebo	53.4	19.3	NR	99	0	
Choueiri et al (2012)[56]	Urothelial cancer	III	142	Vandetanib 100 mg qd po q3w + Doc	NR	2.56	5.85	70	3	Infections
				Placebo + Doc	NR	1.58	7.03	72	4	
Goncalves et al (2012)[57]	Pancreatic cancer	III	104	Sorafenib 400 mg bid po + gemcitabine	64	3.8		52	0	Febrile neutropenia
				Gemcitabine	64	5.7		52	2	
Scagliotti et al (2012)[41]	NSCLC	III	1,090	Motesanib 125 mg qd po + PTX + CBP	60	5.6	13	533	43	Febrile neutropenia, pneumonia
				Placebo + PTX + CBP	60	5.4	11	539	22	
Yi et al (2012)[58]	Gastric cancer	II	107	Sunitinib 37.5 mg qd po + Doc	54	3.9	8	56	15	Febrile neutropenia
				Doc	52	2.6	6.6	49	8	
Hoff et al (2012)[49]	CRC	III	860	Cediranib 20 mg qd po + chemotherapy	58	8.6	19.7	500	5	Pneumonia, septic shock
				Placebo + chemotherapy	59	8.3	18.9	358	3	
Scagliotti et al (2012)[42]	NSCLC	III	960	Sunitinib 37.5 mg qd po + erlotinib	61	3.6	9	473	1	Respiratory tract infection
				Erlotinib	61	2	8.5	477	0	

(*Continued*)

Table 2 (*Continued*)

Authors (year)	Histology	Phase	Patients enrolled	Treatment arm	Median age (years)	Median PFS (months)	Median OS (months)	Number for analysis	Severe infections	Reported infectious events
Carrato et al (2013)[48]	CRC	III	768	Sunitinib 37.5 mg qd po + FOLFIRI	59	7.8	20.3	384	32	Neutropenic sepsis, febrile neutropenia, pneumonia, sepsis/septic shock
				Placebo + FOLFIRI	58	8.4	19.8	384	14	
Grothey et al (2013)[14]	CRC	III	1,052	Regorafenib 160 mg qd po	61		6.4	505	6	Fever, pneumonia
				Placebo	61		5	253	2	
Demetri et al (2013)[15]	GIST	III	199	Regorafenib 160 mg qd po	60	4.8	NR	132	3	Fever
				Placebo	61	0.9	NR	66	0	
Serve et al (2013)[61]	AML	III	162	Sorafenib 400 mg bid po + chemotherapy	NR	7	15	80	15	Pneumonia, sepsis
				Placebo + chemotherapy	NR	5	13	82	4	
Flaherty et al (2013)[59]	Melanoma	III	823	Sorafenib 400 mg bid po + PTX + CBP	66	4.9	11.3	393	24	Febrile neutropenia
				Placebo + PTX + CBP	61	4.2	11.1	397	16	
Brose et al (2014)[50]	Thyroid cancer	III	417	Sorafenib 400 mg bid po	63	10.8	NR	207	3	Fever
				Placebo	63	5.8	NR	209	0	
Garon et al (2014)[40]	NSCLC	III	1,253	Ramucirumab 10 mg/kg + Doc	62	4.5	10.5	627	100	Febrile neutropenia
				Placebo + Doc	61	3	9.1	618	62	
Kudo et al (2014)[53]	HCC	III	502	Brivanib 800 mg qd + TACE	57	12	26.4	246	2	Bacterial peritonitis, pulmonary infection
				Placebo + TACE	59	10.9	26.1	253	0	
Laurie et al (2014)[39]	NSCLC	III	306	Cediranib 20 mg qd po + PTX + CBP	63	5.5	12.2	153	9	Febrile neutropenia
				Placebo + PTX + CBP	62	5.5	12.1	153	5	
Reck et al (2014)[38]	NSCLC	III	655	Nintedanib 200 mg bid po + Doc	60	3.4	10.9	655	66	Febrile neutropenia
				Placebo + Doc	60	2.7	7.9	659	45	
Hutson et al (2014)[60]	RCC	III	512	Sorafenib 400 mg bid po	61	3.9	16.6	252	7	Pneumonia
				Temsirolimus	60	4.3	12.3	249	5	
Michaelson et al (2014)[62]	CRPC	III	873	Sunitinib 37.5 mg qd po + prednisone	69	5.6	13.1	581	3	Pneumonia, sepsis
				Placebo + prednisone	68	4.1	11.8	285	1	

Abbreviations: PFS, progression-free survival; OS, overall survival; NSCLC, non-small-cell lung cancer; qd, once daily; po, per oral; Doc, docetaxel; ABC, advanced breast cancer; bid, twice daily; PTX, paclitaxel; CBP, carboplatin; HCC, hepatocellular carcinoma; NR, not reported; q3w, every 3 weeks; CRC, colorectal cancer; FOLFIRI, folinic acid (leucovorin), fluorouracil, and irinotecan; GIST, gastrointestinal stromal tumor; AML, acute myeloid leukemia; TACE, transcatheter arterial chemoembolization; RCC, renal cell carcinoma; CRPC, castration-resistant prostate cancer.

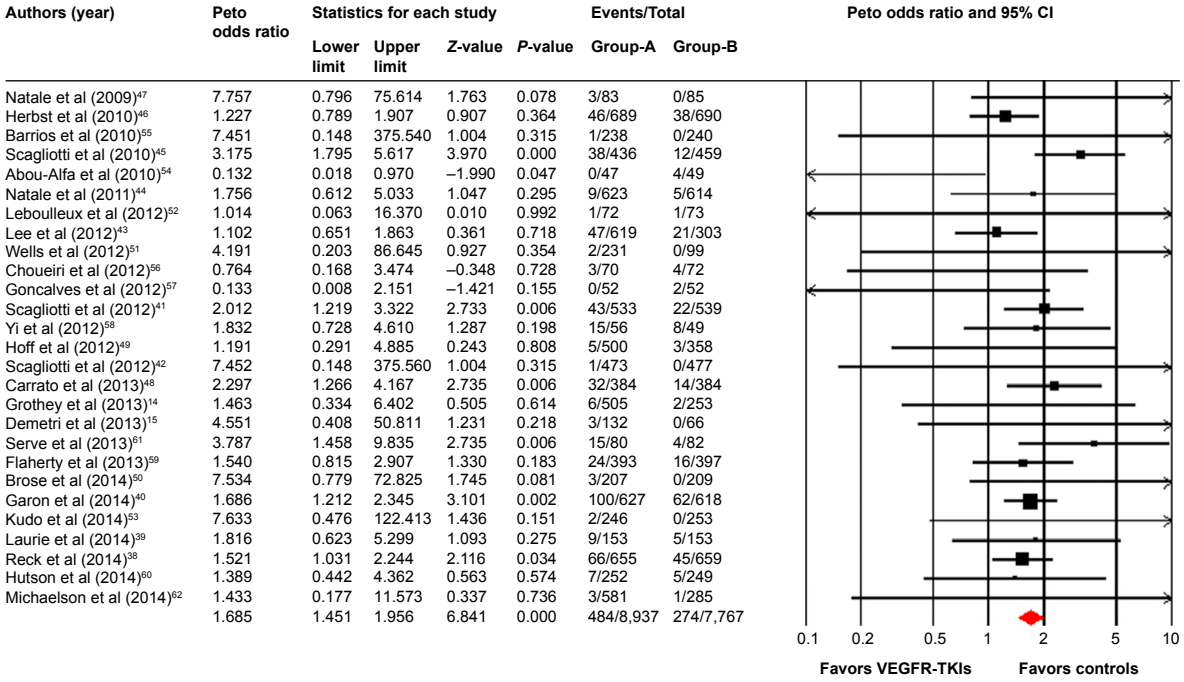

Figure 2 Peto odds ratio of severe infections associated with VEGFR-TKIs vs control.
Abbreviations: VEGFR-TKIs, vascular endothelial growth factor receptor tyrosine kinase inhibitors; CI, confidence interval.

among these tumor types (P=0.85). Clinicians should be cautious when interpreting these results due to the limited RCTs of HCC and colorectal cancer included for the OR calculation.

The risk of severe infections might be related to different VEGFR-TKIs. Our results demonstrated that the use of sorafenib (OR 2.11, 95% CI: 1.48–3.00, P<0.011) and sunitinib (OR 2.18, 95% CI: 1.35–3.53, P=0.001) significantly increased the risk of severe infections, while a nonsignificantly increased risk of severe infections was observed in vandetanib, cediranib, and regorafenib (Table 1). Again, no significant differences in ORs of severe infections were found among these drugs (P=0.48). Then, we also carried out a subgroup risk analysis stratified according to phase of trials (Phase II vs Phase III). Patients from Phase III trials had an OR of 1.71 (95% CI: 1.47–1.99, P<0.001), while patients from Phase II studies had an OR of 1.21 (95% CI: 0.60–2.44, P=0.60; Table 1).

TSA assessed the effect of VEGFR-TKIs on severe infections in cancer patients and showed that the required information size was 3,259 which was less than that in our study (n=16,488), and the cumulative Z-curve crossed the trial sequential monitoring boundary for harm, indicating that further studies are unlikely to change the current conclusion (Figure 5).

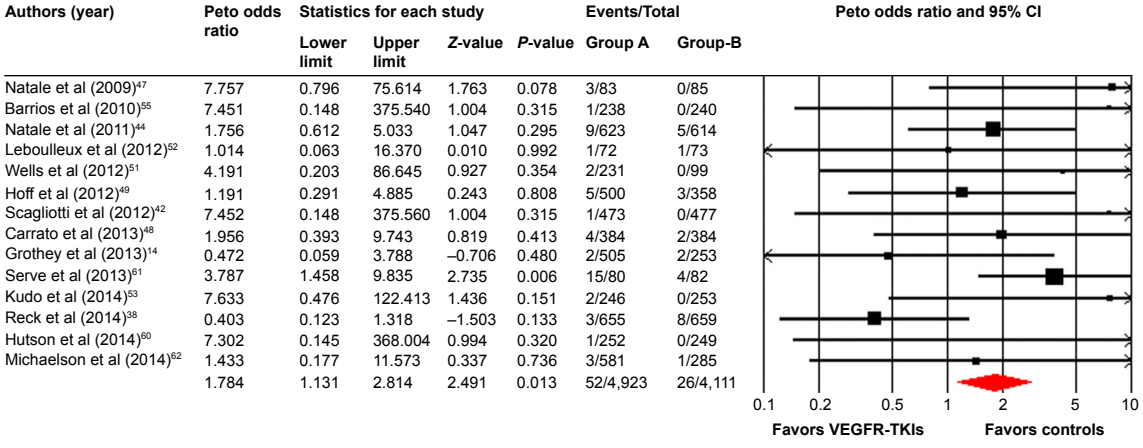

Figure 3 Peto odds ratio of fatal infections associated with VEGFR-TKIs vs control.
Abbreviations: VEGFR-TKIs, vascular endothelial growth factor receptor tyrosine kinase inhibitors; CI, confidence interval.

Authors (year)	Point	Statistics with study removed			
		Lower limit	Upper limit	*Z*-value	*P*-value
Natale et al (2009)[47]	1.674	1.441	1.944	6.740	0.000
Herbst et al (2010)[46]	1.756	1.498	2.058	6.944	0.000
Barrios et al (2010)[55]	1.681	1.448	1.952	6.808	0.000
Scagliotti et al (2010)[45]	1.608	1.377	1.877	6.011	0.000
Abou-Alfa et al (2010)[54]	1.709	1.471	1.986	7.010	0.000
Natale et al (2011)[44]	1.683	1.447	1.958	6.761	0.000
Leboulleux et al (2012)[52]	1.687	1.453	1.960	6.850	0.000
Lee et al (2012)[43]	1.749	1.496	2.044	7.028	0.000
Wells et al (2012)[51]	1.681	1.447	1.952	6.803	0.000
Choueiri et al (2012)[56]	1.698	1.461	1.973	6.909	0.000
Goncalves et al (2012)[57]	1.697	1.461	1.971	6.927	0.000
Scagliotti et al (2012)[41]	1.656	1.416	1.936	6.313	0.000
Yi et al (2012)[58]	1.681	1.445	1.956	6.721	0.000
Hoff et al (2012)[49]	1.691	1.455	1.966	6.854	0.000
Scagliotti et al (2012)[42]	1.681	1.448	1.952	6.808	0.000
Carrato et al (2013)[48]	1.650	1.414	1.926	6.358	0.000
Grothey et al (2013)[14]	1.687	1.452	1.961	6.825	0.000
Demetri et al (2013)[15]	1.678	1.445	1.949	6.778	0.000
Serve et al (2013)[61]	1.651	1.419	1.920	6.493	0.000
Flaherty et al (2013)[59]	1.694	1.452	1.975	6.716	0.000
Brose et al (2014)[50]	1.674	1.441	1.944	6.741	0.000
Garon et al (2014)[40]	1.684	1.425	1.992	6.098	0.000
Kudo et al (2014)[53]	1.677	1.444	1.948	6.773	0.000
Laurie et al (2014)[39]	1.682	1.447	1.956	6.754	0.000
Reck et al (2014)[38]	1.715	1.459	2.016	6.529	0.000
Hutson et al (2014)[60]	1.690	1.454	1.965	6.826	0.000
Michaelson et al (2014)[62]	1.686	1.452	1.959	6.834	0.000
	1.685	1.451	1.956	6.841	0.000

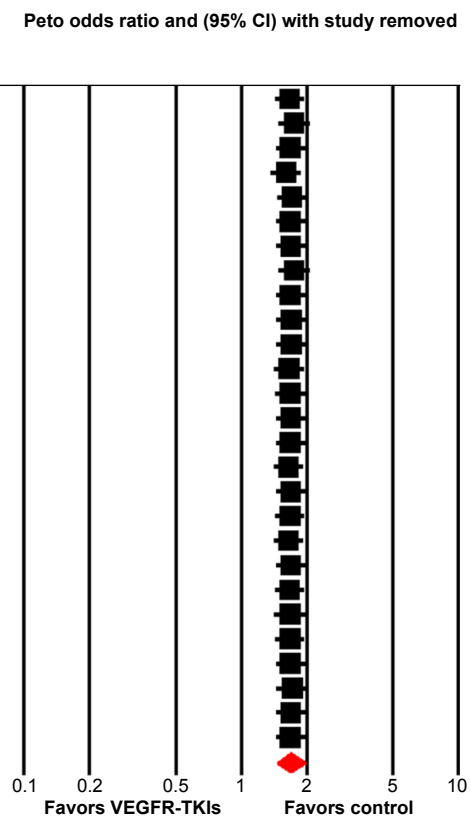

Figure 4 Meta-analysis of severe infections associated with VEGFR-TKIs vs control: "leave-one-out" sensitivity analysis.
Abbreviations: VEGFR-TKIs, vascular endothelial growth factor receptor tyrosine kinase inhibitors; CI, confidence interval.

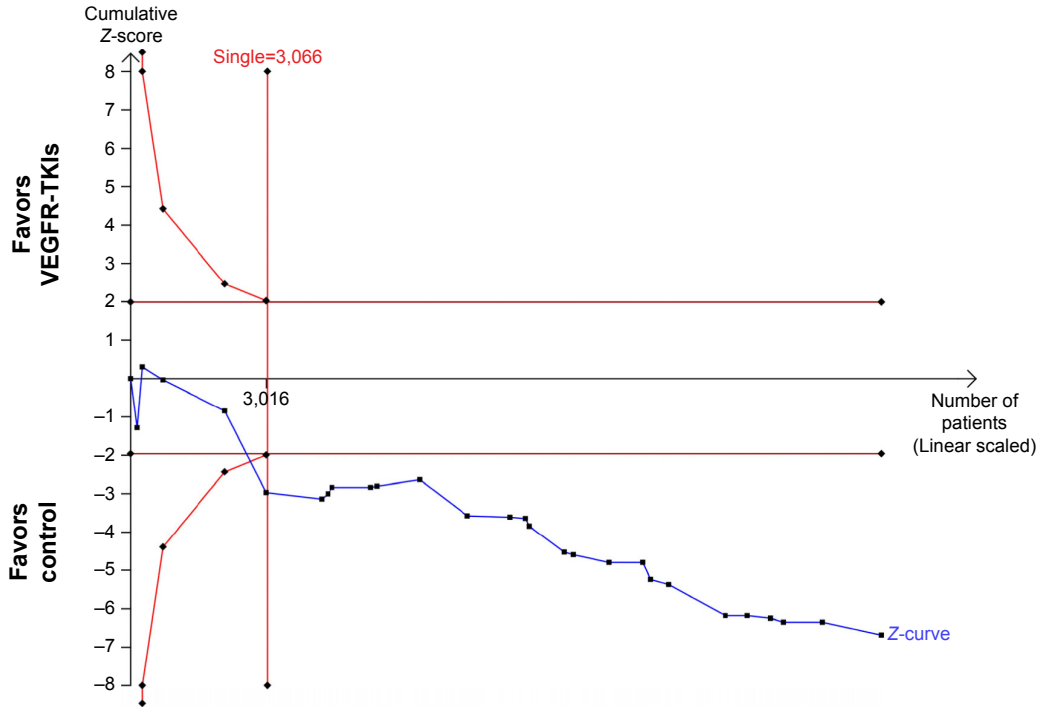

Figure 5 Trial sequential analysis of 27 trials with lower risk of bias reporting severe infections.
Abbreviation: VEGFR-TKIs, vascular endothelial growth factor receptor tyrosine kinase inhibitors.

Table 3 Severe and fatal infectious events with VEGFR-TKIs by specific types

	Infectious events, n/total, n		RR (95% CI)	*P*-value
	VEGFR-TKIs	Control		
Severe infections				
Unspecified	57/1,125	28/834	1.53 (0.98–2.39)	0.062
Febrile neutropenia	298/4,025	195/4,049	1.57 (1.30–1.88)	<0.001
Pneumonia	102/6,273	48/5,172	1.79 (1.29–2.49)	<0.001
Fever	10/844	0/528	5.35 (1.47–19.51)	0.011
Sepsis	17/2,097	3/1,533	3.68 (1.51–8.99)	0.004
Fatal infections				
Pneumonia	36/4,685	24/3,871	1.34 (0.80–2.25)	0.26
Sepsis	16/1,866	3/1,434	3.66 (1.47–9.13)	0.005
Overall	52/4,923	27/4,111	1.78 (1.13–2.81)	0.013

Abbreviations: VEGFR-TKIs, vascular endothelial growth factor receptor tyrosine kinase inhibitors; RR, relative risk; CI, confidence interval.

Risk of severe and fatal infections by specific types

Individual specified and nonspecified causes of severe and fatal infections are listed in Table 3. Of those severe infections that were specified, the most common events for severe infections were febrile neutropenia (61.6%). We then calculated the risk of severe infections stratifying trials according to specific type of severe infections. Our results showed that the use of VEGFR-TKIs significantly increased the risk of severe febrile neutropenia (OR 1.57, 95% CI: 1.30–1.88, $P<0.001$), pneumonia (OR 1.79, 95% CI: 1.29–2.49, $P<0.001$), fever (OR 5.35, 95% CI: 1.47–19.51, $P=0.011$), and sepsis (OR 3.68, 95% CI: 1.51–8.99, $P=0.004$). We also calculated the risk of fatal infections stratifying trials according to specific types of infections; the use of VEGFR-TKIs significantly increased the risk of fatal sepsis (OR 3.66, 95% CI: 1.47–9.13, $P=0.005$) but not fatal pneumonia (OR 1.34, 95% CI: 0.80–2.25, $P=0.26$; Table 1).

Publication bias

A funnel plot and both Begg's and Egger's tests were performed to assess the publication bias of the selected studies. The shapes of the funnel plots showed no evidence of obvious asymmetry ($P=0.61$ for OR of severe infections; Figure 6). The results from Egger's test were not significant ($P=0.58$).

Discussion

During the past decade, identification of the importance of VEGF signal pathway in tumor growth, invasion, and metastasis has led to the development of VEGFR-targeted treatments, which has significantly changed the prognosis of several solid tumors including RCC, HCC, colorectal cancer, and thyroid cancer. Although VEGFR-TKIs are generally well tolerated, infection is an emerging complication with the use of these drugs. Infections can delay treatment or reduce patient compliance with VEGFR-TKI therapies, and the management of infections also increases the cost of cancer treatment. Thus, it is particularly important for all health care practitioners and patients to understand and recognize the risk of infection associated with VEGFR-TKI therapies.

To the best of our knowledge, this is the first and largest meta-analysis evaluating the risk of infections associated with VEGFR-TKIs. In this comprehensive analysis of 16,488 patients, 27 randomized Phase II and III trials using VEGFR-TKIs (sunitinib, sorafenib, pazopanib, axitinib, vandetanib, cediranib, ramucirumab, regorafenib, nintedanib, and motesanib) were included. We did not include Phase I trials in our meta-analysis, since these studies are not randomized and include a wide range of different dosages of drugs. We observed a significant 1.69-fold increase in the risk of high grades of infections with VEGFR-TKIs compared to controls not receiving VEGFR-TKIs. Sensitivity analysis demonstrated that the significance estimate of pooled severe ORs was not significantly influenced by omitting any single study. We also investigated the outcome

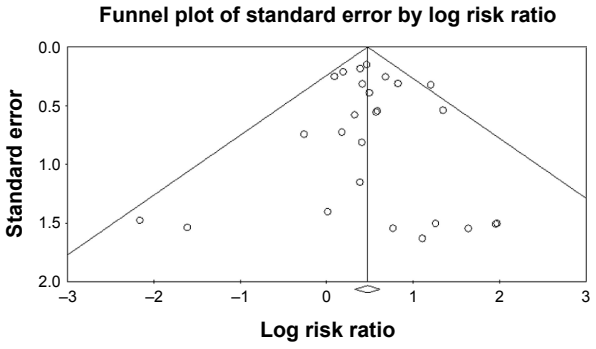

Figure 6 Funnel plot of standard error by log-risks ratio for severe infections.

of VEGFR-TKIs-associated severe infections; our results showed that the use of VEGFR-TKIs significantly increased the risk of fatal infections when compared to non-VEGFR-TKI regimens (P=0.013). However, given that the absolute risk of fatal infections is low, the use of VEGFR-TKIs should be considered in the context of overall survival benefits. As VEGFR-TKIs are increasingly used in cancer patients, it is particularly important for clinicians to understand and recognize the risk of severe and fatal infection.

Given an increased OR of treatment-related infections, it is clear that proper monitoring, immediate intervention, and effective management are crucial to achieve the maximal therapeutic benefit of VEGFR-TKIs. However, there are no specific guidelines for the treatment of VEGFR-TKIs-induced infections because there is a lack of controlled studies addressing the subject. Based on our findings, the following approaches may be considered to reduce the association of VEGFR-TKIs with risk of infections. Before the initiation of VEGFR-TKIs, clinicians must fully treat patients with any active infection and must monitor patients during the course of VEGFR-TKIs treatment. Clinicians should be cautious when adding VEGFR-TKIs, especially sorafenib and sunitinib, to the first-line or second-line therapies for the treatment of NSCLC and colorectal cancers.

Despite the size of this meta-analysis, our study has some limitations. First, this was a trial-level meta-analysis, and confounding variables at the patient level, such as comorbidities, younger age, prior cardiac history, and previous chemotherapeutic exposure, could not be incorporated into the analysis. However, all of the included trials exhibited moderate- or good-quality Jadad scores, and a report suggests that trial-level and patient-level meta-analyses yield similar results. Second, although most of these trials carried out the randomization process adequately, the infectious events are retrospectively collected. Therefore, these data should be interpreted cautiously because the extracted data used for this analysis could not be considered randomized, which somehow compromised the evidence level. Finally, our literature search is limited to articles published in English creating some selection bias. However, our research detects no publication bias using Begg and Egger tests for ORs of severe and fatal infections.

Conclusion

The use of small-molecule VEGFR-TKIs is associated with an increase in the risk of developing severe and fatal infectious events in cancer patients. Close monitoring for any sign of infections is recommended, especially in NSCLC and colorectal cancer patients. Nevertheless, for the average patient, these approved drugs do improve clinical outcomes in their respective indications, and the benefits generally outweigh the risks.

Authors' contributions

QM and D-SZ designed research. L-YG, YYR, and L-LZ conducted research. TG, D-SZ, and YYR analyzed data. QM wrote the draft. All authors read, reviewed, and approved the final manuscript. D-SZ had primary responsibility for final content. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

All authors declare that they have no potential conflicts of interests.

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Supplementary materials

Search strategy for meta-analysis of association between use of vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKIs) and the risk of severe infections in cancer patients

PubMed

1. VEGFR-TKIs [ALL]
2. "VEGFR-tyrosine kinase inhibitors" [ALL]
3. "VEGFR-tyrosine kinase inhibitor" [ALL]
4. "vascular endothelial growth factor receptor tyrosine kinase inhibitor" [ALL]
5. "vascular endothelial growth factor receptor tyrosine kinase inhibitors" [ALL]
6. 1 or 2 or 3 or 4 or 5
7. "nexavar" [NM] OR "BAY43-9006" [NM] OR "sorafenib" [ALL]
8. "sutent" [NM] OR "SU11248" [NM] OR "sunitinib" [ALL]
9. "votrient" [NM] OR"GW786034" [NM] OR "vandetanib" [ALL]
10. "caprelsa" [NM] OR "ZD6474" [NM] OR "axitinib" [ALL]
11. "AG-013736" [MH] OR "cediranib" [ALL]
12. "AZD2171" [NM] OR "tivozanib" [ALL]
13. "BAY73-4506" [MH] OR "regorafenib" [ALL]
14. "cabozantinib" [ALL]
15. "brivanib" [ALL]
16. "ramucirumab" [ALL]
17. "IMC-1121B" [NM] OR "nintedanib" [ALL]
18. "BIBF1120" [MH] OR "motesanib" [ALL]
19. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
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21. "neoplasm" [ALL]
22. "neoplasia" [ALL]
23. "malignancy" [ALL]
24. Malignant [ALL]
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30. "meningioma" [MH] OR "meningioma" [ALL]
31. "sarcoma" [MH] OR "sarcoma" [ALL]
32. 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
33. 19 and 32
34. "humans" [MH]
35. 33 and 34

ALL = all fields, MH = MeSH Terms, NM = substance name

Limitation: humans

Date of Search: December 2014 (1974–December 2014)

EMBASE

1. VEGFR-TKIs
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5. "vascular endothelial growth factor receptor tyrosine kinase inhibitors"/de
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19. "motesanib"/de
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24. malignancy
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27. "glioma"/de
28. "leukemia"/de
29. "lymphoma"/de
30. "melanoma"/de
31. "meningioma"/de
32. "sarcoma"/de
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35. [embase]/lim OR [embase classic]/lim
36. 20 and 34 and 35

/de = Mapped terms, /lim = Limitation

Limitation: humans

Date of Search: December 2014 (1979–December 2014)

CENTRAL database (The Cochrane Library)

1. VEGFR-TKIs [ALL]
2. "VEGFR-tyrosine kinase inhibitors" [ALL]
3. "VEGFR-tyrosine kinase inhibitor" [ALL]
4 "vascular endothelial growth factor receptor tyrosine kinase inhibitor" [ALL]
5. "vascular endothelial growth factor receptor tyrosine kinase inhibitors" [ALL]
6. 1 or 2 or 3 or 4 or 5
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33. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
34. 20 and 33

[ALL] = in All Text

Limitation: none

Date of Search: December 2014 (1979–December 2014)