Incidence and risk of hypertension with a novel multi-targeted kinase inhibitor axitinib in cancer patients: a systematic review and meta-analysis

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The use of vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs) is associated with an increased risk of developing hypertension. Axitinib is a novel, selective VEGFR-TKI, but its overall incidence and risk of developing hypertension is still unknown.

WHAT THIS STUDY ADDS

- The use of axitinib is associated with an unexpectedly high risk of developing hypertension when compared with the other four approved VEGFR-TKIs. Close monitoring and appropriate management for hypertension are recommended during treatment.

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AIMS

To investigate the overall incidence and risk of hypertension in cancer patients who receive axitinib and compare the differences in incidences between axitinib and the other four approved vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs).

METHODS

Several databases were searched, including Pubmed, Embase and Cochrane databases. Eligible studies were phase II and III prospective clinical trials of patients with cancer assigned axitinib at a starting dose of 5 mg orally twice daily with data on hypertension available. Overall incidence rates, relative risk (RR), and 95% confidence intervals (CI) were calculated employing fixed or random effects models depending on the heterogeneity of the included trials.

RESULTS

A total of 1908 patients from 10 clinical trials were included. The overall incidences of all grade and high grade hypertension in cancer patients were 40.1% (95% CI 30.9, 50.2%) and 13.1% (95% CI 6.7, 24%). The use of axitinib was associated with significantly increased risk of all grade (RR 3.00, 95% CI 1.29, 6.97, $P = 0.011$) and high grade hypertension (RR 1.71, 95% CI 1.21, 2.43, $P = 0.003$). The risk of axitinib associated all grade and high grade hypertension in renal cell carcinoma (RCC) was significantly higher than that in non-RCC. Additionally, the risk of hypertension with axitinib was substantially higher than other approved VEGFR-TKIs, while the risk of all grade hypertension with axitinib was similar to pazopanib (RR 1.05; 95% CI 0.95-, 1.17, $P = 0.34$).

CONCLUSIONS

While sharing a similar spectrum of target receptors with other VEGFR-TKIs, axitinib is associated with an unexpectedly high risk of developing hypertension. Close monitoring and appropriate management for hypertension are recommended during the treatment.

Introduction

Vascular endothelial growth factor (VEGF) plays an important role in tumour growth, invasion and metastasis by promoting angiogenesis, and the blockade of its signalling pathway has become a major approach for cancer treatment [1]. Axitinib (AG-013736; Inlyta; Pfizer Inc., New York, USA), an oral, potent, selective tyrosine kinase inhibitor of vascular endothelial growth factor receptor-1 (VEGFR-1), VEGFR-2 and VEGFR-3 [2], has recently been approved by the US Food and Drug Administration in January 2011 for the treatment of advanced renal cell carcinoma (RCC) after failure of one prior systemic therapy [3]. Currently, axitinib is undergoing wide investigation as a single agent or in combination with chemotherapy for the treatment of other solid tumours such as pancreatic cancer [4, 5], advanced non-small-cell lung cancer (NSCLC) [6] and melanoma [7]. As a result, the use of axitinib is expected to increase in the near future and an appreciation of the toxicity profiles of axitinib is therefore urgently needed.

Similar to the other four approved VEGFR tyrosine kinase inhibitor (TKIs) (sorafenib, sunitinib, vandetanib and pazopanib), the common adverse events of axitinib are diarrhoea, nausea, fatigue and hand-foot syndrome [8]. Although hypertension is also described to be a frequent adverse event for axitinib, the reported incidences vary substantially among clinical trials (all grade: 21.7% to 84.4%; high grade: 4.5% to 70.3%) [5, 9, 10]. Moreover, previous meta-analyses have demonstrated that the use of VEGFR-TKIs (sorafenib, sunitinib, vandetanib and pazopanib) was associated with an increased risk of developing hypertension [11–14], but the contribution of axitinib to hypertension remains poorly defined due to a limited number of patients included in the trials. As with other angiogenesis inhibitors, the mechanisms of axitinib-induced hypertension may be directly related to its inhibitory effect on VEGF signal pathways [15], resulting in a reduced density of microvessels, endothelial dysfunction associated with reduced nitric oxide (NO) production and increased oxidative stress [15–17], and changes in neuro-hormonal factors [17]. Because poorly controlled hypertension may lead to serious cardiovascular events, dose reduction and life-threatening consequences, determining the risk of axitinib associated hypertension is of special importance [18]. In addition, exploring the differences in the occurrence of hypertension among VEGFR-TKIs may offer additional insight into the understanding of underlying mechanisms, risk factors and potential management strategies. Therefore, we conducted this meta-analysis of all published trials to determine the overall incidence and risk, and compare the differences in incidences between axitinib and the other four approved VEGFR-TKIs.

Methods

Search strategy

We searched the Pubmed (data from 1966 to Jan 2013), Embase (data from 1980 to January 2013) and the Cochrane Library electronic databases. Keywords included in the search were 'axitinib', 'Inlyta', 'AG-013736', 'cancer', 'randomized' and 'hypertension'. The search was restricted to clinical trials and articles published in English. Additionally, we searched the clinical trial registration website (<http://www.ClinicalTrials.gov>) to obtain information on the registered randomized controlled trials (RCTs). The updated manufacturer package insert of axitinib was also reviewed for related information.

Study selection

Two investigators independently assessed the eligibility of the articles and abstracts identified by the search, and discrepancies were resolved by consensus. Axitinib had been approved for use in patients with advanced RCC as a single agent at a recommended starting dose of 5 mg taken orally twice daily. The dose could be increased to 7 mg twice daily in patients who tolerated the starting dose for 2 weeks, and did not present with grade 2 adverse events. The treatment dose can be further increased to 10 mg twice daily according to the same criteria. On the other hand, when adverse events require dose reductions, axitinib may be decreased to 3 mg twice daily, and further to 2 mg twice daily [19]. Nevertheless, it is clinically significant to determine the risk of hypertension in cancer patients receiving the approved doses of axitinib for various malignancies. Phase I trials with axitinib were excluded from analyses due to multiple dose levels and limited sample sizes. The clinical trials that met the following criteria were selected for the final analysis: (1) prospective phase II and III clinical trials in cancer patients, (2) participants assigned to treatment with axitinib at a starting dosage of 5 mg orally twice daily [3] and (3) events or event rate and sample size available for hypertension. If multiple publications of the same trial were retrieved or if there was a case mix among publications, only the most recent publication (and the most informative) was included.

Clinical end points

Hypertension was extracted from the safety profile in each trial. These clinical end points were recorded according to version III of the Common Terminology Criteria for Adverse Events (CTCAE) of National Cancer Institute (http://ctep.cancer.gov/reporting/ctc_archive.html) [20]. The CTC 3.0 version describes the grading of hypertension as grade I, asymptomatic, transient (<24 h) increase of blood pressure by >20 mmHg (diastolic) or to >150/100 mmHg if previously within normal limit (WNL), intervention not indicated, grade II, recurrent or persistent (>24 h) or symp-

Figure 1

Flow chart of trial selection process in the meta-analysis

tomatic increase by >20 mmHg (diastolic) or to >150/100 mmHg if previously WNL, monotherapy may be indicated, grade III, requiring more than one drug or more intensive therapy than previously and grade IV, hypertensive crisis. We included all incidences of hypertension of grade 1 or above in our analysis.

Data analysis

The data of the number of patients with all grades and high grades (grade 3 and grade 4) of hypertension and the number of patients receiving axitinib were extracted from the adverse events outcomes. For each study, we derived the proportion and 95% confidence interval (CI) of patients with hypertension. For studies with a control group in the same trial, we also calculated and compared the relative risk (RR) of hypertension. For one study that reported zero events in the control arm, we applied the classic half-integer correction to calculate the RR and variance [21]. Between-study heterogeneity was estimated using the χ^2 -based Q statistic [22]. Heterogeneity was considered statistically significant when $P_{\text{heterogeneity}} < 0.05$ or $I^2 > 50\%$. If heterogeneity existed, data were analyzed using a random effects model. In the absence of heterogeneity, a fixed effects model was used. To calculate the pooled incidence, an inverse variance statistical method was used. A statistical test with a P value less than 0.05 was considered significant. The presence of publication bias was evaluated by using the Begg and Egger tests [23, 24]. All statistical analyses were performed by using Stata version 12.0 software (Stata Corporation, College Station, Texas, USA) and Open

Meta-Analyst software version 4.16.12 (Tufts University, URL http://tuftscaes.org/open_meta/).

Results

Search results

Our search yielded a total of 216 articles on axitinib from the literature. After reviewing each publication, we identified 10 original studies that met our inclusion criteria, including two phase III trials and eight phase II trials (Figure 1). A total of 1908 patients from 10 clinical trials were available for analysis. The baseline characteristics of patients in the 10 studies are listed in Table 1. Underlying malignancies for these trials included metastatic RCC [9, 19, 25, 26] (four trials), metastatic melanoma [7] (one trial), metastatic breast cancer [10] (one trial), advanced NSCLC [6] (one trial), pancreatic cancer [4, 5] (two trials) and all histological subtypes of advanced thyroid cancer [27] (one trial). Hypertension was not described as a pre-existing condition in any of the trials.

Incidence of all grade hypertension

A total of 1148 patients from 10 trials were included for this analysis. The majority of these patients had either RCC or pancreatic cancer. The reported incidence of all grade hypertension ranged from 21.7 to 84.4%. The lowest incidence was noted in a phase II single arm trial among patients with pancreatic cancer [5] and the highest incidence was observed in patients with RCC [9]. The

Table 1
Baseline characteristics of 10 trials included in the meta-analysis

Study	Phase	Underlying malignancy	Treatment arms	Patients included for analysis	Median age (years)	Female (%)	Median PFS (months)	Median OS (months)	Number of high grade hypertension events	CTC version
Rixe <i>et al</i> 2007 [26]	II	RCC	Axitinib 5 mg twice daily orally	52	59	23	15.7	29.9	8	3.0
Cohen <i>et al</i> 2008 [27]	II	Thyroid cancer	Axitinib 5 mg twice daily orally	60	59	42	18.1	NR	7	3.0
Spano <i>et al</i> 2008 [5]	II	Pancreatic cancer	Axitinib 5 mg twice daily orally plus GEM.	69	65	49	4.2	6.9	4	3.0
			GEM	34	61	53	3.7	5.6	0	
Rini <i>et al</i> 2009 [25]	II	RCC	Axitinib 5 mg twice daily orally	62	60	32.3	7.4	13.6	10	3.0
Schiller <i>et al</i> 2009 [6]	II	NSCLC	Axitinib 5 mg twice daily orally	32	66.5	41	4.9	14.8	3	3.0
Fruehauf <i>et al</i> 2011 [7]	II	Melanoma	Axitinib 5 mg twice daily orally	32	65	46.9	3.9	6.6	3	3.0
Kindler <i>et al</i> 2011 [4]	III	Pancreatic cancer	Axitinib 5 mg twice daily orally plus GEM	305	61	39	4.4	8.5	20	3.0
			Placebo plus GEM	308	62	41	4.4	8.3	5	
Rini <i>et al</i> 2011 [19]	III	RCC	Axitinib 5 mg twice daily orally	361	61	27	6.7	NR	56	3.0
			Sorafenib 400 mg twice daily orally	362	61	29	4.7	NR	39	
Rugo <i>et al</i> 2011 [10]	II	MBC	Axitinib 5 mg twice daily orally plus TXT	111	55	100	8.1	NR	5	3.0
			Placebo plus TXT	56	56	100	7.1	NR	0	3.0
Tomita <i>et al</i> 2011 [9]	II	RCC	Axitinib 5 mg twice daily orally	64	63	31	11	NR	45	3.0

CTC, common toxicity criteria; GEM, gemcitabine; MBC, metastatic breast cancer; NR: not reported; NSCLC, non-small-cell lung cancer; RCC, renal cell carcinoma; TXT, docetaxel.

Figure 2

Forest plot for meta-analysis of incidence of all grade hypertension in cancer patients assigned axitinib

Figure 3

Forest plot for meta-analysis of incidence of high grade hypertension in cancer patients assigned axitinib

meta-analysis revealed significant heterogeneity between the included studies ($I^2 = 88\%$, $P < 0.001$), and the calculated summary incidence of all grade hypertension among patients receiving axitinib was 40.1% (95% CI 30.9, 50.2%, Figure 2) using a random effects model.

Incidence of high grade hypertension

High grade (grade 3 or 4) hypertension was associated with significant morbidity, and might result in dose reduction or discontinuation of axitinib. All of the 10 trials reported incidence of high grade hypertension data, and the incidence of high grade hypertension ranged from 4.5 and 70.3%, with the highest incidence seen in the phase II trial by Tomita *et al.* in Japanese patients with metastatic RCC [9] and the lowest incidence observed in patients with metastatic breast cancer [10]. The calculated summary incidence of high grade hypertension among 1148 patients

receiving axitinib was 13.1% (95% CI 6.7, 24.0%, Figure 3) using the fixed effects model ($I^2 = 93\%$, $P < 0.001$).

Relative risk of hypertension

To investigate the specific contribution of axitinib to the development of hypertension and exclude the influence of confounding factors such as underlying malignancy and other therapeutic interventions, we therefore determined the relative risk (RR) of axitinib-induced hypertension. The pooled RR for all grade hypertension showed that treatment with axitinib significantly increased the risk of developing all grade hypertension in cancer patients with RR 3.00 (95% CI 1.29, 6.97, $P = 0.011$, Figure 4) using a random effects model ($I^2 = 84\%$, $P < 0.001$). As for high grade hypertension in patients prescribed axitinib, the combined RR also demonstrated that axitinib was associated with a significantly increased risk of high grade hypertension among

Figure 4

Relative risk of axitinib-associated all grade hypertension vs. control from randomized controlled trials of patients with cancer

Figure 5

Relative risk of axitinib-associated high grade hypertension vs. control from randomized controlled trials of patients with cancer

cancer patients (RR 1.71, 95% CI 1.21, 2.43, $P = 0.003$, Figure 5) using a fixed effects model ($I^2 = 39\%$, $P = 0.18$).

Incidence of hypertension in patients with RCC vs. non-RCC malignancy

In order to explore the relationship between axitinib-associated hypertension and tumour types, we further analyzed the incidence of hypertension in patients with RCC and non-RCC cancers. Among patients with RCC, the summary incidences of all grade and high grade hypertension was 57.6% (95% CI 38.3, 74.9%) and 26.1% (95% CI 8.9, 56%), respectively, using a random effects model; while for those patients with non-RCC malignancies, the summary incidences of all grade and high grade were 28.4% (95% CI 24.8, 32.4%) and 7.2% (95% CI 5.3, 9.5%) using a random effects model. Interestingly, there was a significant difference detected between RCC and non-RCC cancer in terms of the incidence of axitinib-associated all grade hypertension (RR 1.69, 95% CI 1.45, 1.97, $P < 0.001$) and high grade hypertension (RR 3.20, 95% CI 2.30, 4.46, $P < 0.001$).

Difference in hypertension incidence among various approved VEGFR-TKIs

Lastly, we explored the difference in the incidence of hypertension associated with axitinib as compared with the other four approved VEGFR-TKIs. The risk of developing

hypertension with axitinib was substantially higher than with the other four approved VEGFR-TKIs, while the risk of all grade hypertension with axitinib was similar to pazopanib (RR 1.05, 95% CI 0.95, 1.17, $P = 0.34$) (Table 2).

Publication bias

No evidence of publication bias was detected for the incidence or the RR of all grade and high grade hypertension in this study by either Begg test (RR of all grade hypertension: Begg's test $P = 0.317$; Egger's test $P = 0.254$).

Discussion

In a pivotal phase III trial in patients with advanced RCC that had progressed despite first line therapy, axitinib 5 mg twice daily significantly prolonged median progression-free survival compared with sorafenib 400 mg twice daily (6.7 months vs. 4.7 months), and also had a higher response rate [19]. Based on these results, axitinib received approval as second-line therapy for advanced RCC in 2011. Although many of the toxicities of axitinib are shared with those of the other VEGFR-TKIs, there are important differences. Most notably a higher incidence of hypertension seems to occur in axitinib group. However, the overall incidence and risk of axitinib induced hypertension is still unknown. We

Table 2

Comparison of the risk of hypertension between axitinib and other VEGFR-TKIs

Risk subset	Axitinib Incidence (sample size)	Sorafenib* Incidence (sample size)	Relative risk (95% CI)	P value
All grade	40.1% (1148)	23.4% (3363)	1.60 (1.45, 1.76)	$P < 0.0001$
High grade	13.1% (1148)	5.7% (3567)	2.46 (2.03, 3.00)	$P < 0.0001$
Axitinib				
All grade	40.1% (1148)	21.6% (4609)	1.73 (1.58, 1.90)	$P < 0.0001$
High grade	13.1% (1148)	6.8% (4407)	2.06 (1.72, 2.47)	$P < 0.0001$
Axitinib				
All grade	40.1% (1148)	35.5% (1212)	1.05 (0.95, 1.17)	0.34
High grade	13.1% (1148)	6.5% (1286)	2.15 (1.67, 2.76)	$P < 0.0001$
Axitinib				
All grade	40.1% (1148)	24.2% (1815)	1.54 (1.38, 1.73)	$P < 0.0001$
High grade	13.1% (1148)	6.4% (1190)	2.20 (1.69, 2.85)	$P < 0.0001$

*The incidence for VEGFR-TKI associated hypertension are derived from previous systematic reviews [12–15].

thus conducted this meta-analysis to determine its overall incidence and compare the difference in incidences between axitinib and the other four approved VEGFR-TKIs.

Our analysis, based on 1908 patients from 10 clinical trials, demonstrates that the use of axitinib is associated with an increased risk of developing all grade and high grade hypertension in cancer patients. The overall incidence of high grade hypertension with axitinib is higher than with the other four VEGFR-TKIs. The mechanism of developing hypertension may result from the anti-VEGF effect of VEGFR-TKIs. VEGF not only stimulates endothelial cell proliferation, but also promotes endothelial cell survival and helps maintain vascular integrity. Inhibition of VEGF could increase peripheral resistance because of endothelial cell damage and dysfunction [15, 17]. Another important part of the mechanism of hypertension associated with VEGF inhibition is thought to involve decreased production of NO in the wall of arterioles and other resistance vessels. Vascular endothelial growth factor increases NO synthesis through upregulation of endothelial NO synthase and VEGF inhibition diminishes NO synthesis [16, 28]. Because NO is a vasodilator, decreased NO synthesis promotes vasoconstriction, increased peripheral resistance and increased blood pressure [17]. However, as yet, there are limited data on the underlying mechanisms for development of VEGFR-TKI associated hypertension, and studies focusing on this issue are still required. Nevertheless, since patients with cancer are surviving longer, improving the quality of life by reducing complications is an important issue. Hypertension is an independent risk factor for both renal and cardiovascular events [29, 30], and poorly controlled hypertension might lead to serious cardiovascular events, dose reduction and life-threatening consequences.

As a result, it is important that hypertension induced by axitinib be recognized and managed appropriately.

Patients with RCC might have a greater risk of hypertension than those with non-RCC malignancies as a result of a previous nephrectomy and renal dysfunction [31, 32]. Therefore we performed a sub-group analysis to determine the risk of hypertension in RCC and non-RCC. The absolute of risk of developing hypertension is significantly higher in patients with RCC when compared with non-RCC cancers (57.6% vs. 28.4%; RR 1.69, 95% CI 1.45, 1.97, $P < 0.001$). One possible explanation for this finding is that patients with RCC could have higher baseline blood pressure than non-RCC patients, and patients with RCC usually have underlying renal insufficiency, resulting in a decreased clearance of axitinib. Moreover, we also explored the differences in the incidence of hypertension associated with axitinib as compared with other VEGFR-TKIs, and found that the risk of developing hypertension with axitinib was substantially higher than with other VEGFR-TKIs (sorafenib, sunitinib, vandetanib and pazopanib), while the risk of all grade hypertension with axitinib was similar to pazopanib (RR 1.05, 95% CI 0.95, 1.17, $P = 0.34$), which was consistent with the results from a RCT [19]. In that study, the incidence of all grade and high grade hypertension with axitinib was also higher than that with sorafenib (all grade 40% vs. 29%; high grade 16% vs. 11%). The reasons for the higher incidence of hypertension with axitinib as compared with other VEGFR-TKIs might be a difference in spectrum and specificity of target receptors. Axitinib is structurally designed to bind to VEGF receptors with high potency and specificity [2, 33]. The *in vitro* half-maximal inhibitory concentrations (IC_{50}) of axitinib against VEGFR 1–3 were 0.1–0.3 nmol l^{-1} [2]. In contrast, the IC_{50} of

sorafenib, sunitinib and pazopanib against VEGFR 1–3 was at least 10-fold greater, at 2–90 nmol L⁻¹ [33]. The IC₅₀ of axitinib for other non-VEGFR TKIs (e.g. platelet-derived growth factor, colony-stimulating factor, fibroblast growth factor) were 1.6 to >1000 nmol L⁻¹ (vs. 6–880 nmol L⁻¹ for the other agents) [33]. Additionally, previous research has demonstrated that the mechanisms of angiogenesis agent-induced hypertension might be directly related to its inhibitory effect on VEGFR [34]. Therefore, the incidence of hypertension with axitinib is substantially higher than with other VEGFR-TKIs.

Although VEGFR-TKI associated hypertension is a common adverse event noted in clinical trials, the treatment for this adverse event is still under debate. According to a recent expert consensus reported by the Investigational Drug Steering Committee of the National Cancer Institute, blood pressure (BP) should be controlled for approximately 1 week before starting VEGFR-TKI therapy. Hypertension should be monitored and controlled with appropriate antihypertensive agents, with weekly monitoring of BP during the first cycle and 2 to 3 weeks thereafter until a stable BP has been reached, and then monitored as per standard medical practice [15]. Likewise, BP should be monitored following discontinuation of TKI therapy since BP can drop rapidly. Patients who develop stage I hypertension ($\geq 140/90$ mmHg) or have increases in diastolic BP (DBP) ≥ 20 mmHg from baseline should initiate antihypertensive therapy, modify the dose of the current agent for better control, or add a second antihypertensive agent [15]. In some instances, dose reduction of the VEGFR-TKIs can be implemented to manage VEGFR-TKI induced hypertension. The major classes of antihypertensive agents, including angiotensin-converting enzyme (ACE) inhibitors, β -adrenoceptor blockers and calcium channel blockers, have been used to treat TKI-induced hypertension. There are no consensus recommendations, however, for the use of specific antihypertensive agents in this setting [35]. Antihypertensive agents should be individualized to suit the patient's clinical status. ACE inhibitors, for example, are preferred for patients with proteinuria, chronic kidney disease risks or metabolic syndrome [35].

Previous research has demonstrated that the development of hypertension during sunitinib therapy was associated with improved clinical outcomes in patients with RCC, and it could be considered as a potential efficacy marker [36, 37]. However, whether the development of hypertension with axitinib is associated with its antitumour efficacy remains undefined. Data from a retrospective analysis across multiple tumor types showed that patients with elevated DBP ≥ 90 mmHg had a significantly lower relative risk of death than those with DBP <90 mmHg (HR 0.55; 95% CI 0.39, 0.77), and the relative risk of progression was also lower in patients with DBP ≥ 90 mmHg (HR, 0.76; 95% CI: 0.54–1.06) [38]. In addition, a phase II trial conducted by Spano *et al.* [5] showed that patients who devel-

oped diastolic blood pressure (DBP) ≥ 90 mmHg had longer overall survival, compared with those without such change in blood pressure (13.7 months vs. 8.7 months). However, care should be taken in interpreting this result. Analyses in which subsets of patients are based on retrospective or post-randomization outcomes could be biased by imbalances in independent factors that might alter the treatment effect.

A couple of limitations of our meta-analysis should be noted. First, the analysis was based on published aggregated data and not individual patient data, and meta-analyses based on published data tend to overestimate treatment effects compared with individual patient data analyses. In addition, it precluded a more comprehensive analysis, such as adjusting for baseline factors and other differences that existed between the trials from which the data were pooled, although a previous review by Bennett *et al.* [39] showed remarkably similar results between patient level and study level meta-analyses. Secondly, although we only included trials at a starting dose of axitinib 5 mg twice daily, the different studies included have variable numbers of patients who had doses titrated in either direction, and none of included studies specifically commented on how overall daily dose was associated with the occurrence of hypertension. Thirdly, the baseline hypertension of the patients was not described in the included trials, which may have led to an overestimation of the incidence with axitinib. Finally, these studies were conducted at various international institutions by different investigators and may have potential bias in reporting the types of adverse events. In addition, only patients with adequate major organ function are included in these trials, and therefore the results may not reflect the general patient population in the community or patients with organ dysfunction.

Conclusion

While sharing a similar spectrum of target receptors with other VEGFR-TKIs, axitinib is associated with an unexpectedly high risk of developing hypertension. As this drug gains greater clinical use, clinicians should be aware of the possibility that any patient treated with axitinib may develop hypertension, especially those at high risk. Further research is needed to improve our understanding of the underlying pathogenesis and potential risk factors contributing to developing hypertension. Close monitoring and appropriate management for hypertension are recommended during treatment with axitinib.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf

(available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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