Incidence and risk of hypertension with vandetanib in cancer patients: a systematic review and meta-analysis of clinical trials

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AIM

To perform a systematic review and meta-analysis of published clinical trials to determine incidence rate and overall risk of hypertension with vandetanib in cancer patients.

METHODS

A comprehensive literature search for studies published up to March 2012 was performed. Summary 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 11 trials with 3154 patients were included for the meta-analysis. The summary incidences of all-grade and high-grade hypertension in patients with cancer were 24.2% [95% confidence interval (CI), 18.1–30.2%] and 6.4% (95% CI, 3.3–9.5%), respectively. Subgroup analysis demonstrated that the pooled incidences of all-grade and high-grade hypertension were 21.8% [95% CI, 15–30.5%] and 7.6% (95% CI, 2.8–18.8%), respectively, among non-small-cell lung cancer (NSCLC) patients, and 32.1% (95% CI: 27.3–37.3%) and 8.8% (5.9–12.9%), respectively, among MTC patients, and 15.4 (95% CI: 3.2–33.7%) and 3.4% (95% CI: 1%–11.1%) respectively, among non-MTC/NSCLC tumors patients. Furthermore, vandetanib was associated with a significant increased risk of all-grade hypertension (RR 5.1, 95% CI: 3.76–6.92, $P = 0.000$) and high-grade hypertension (RR 8.06, 95% CI: 3.41–19.04, $P = 0.000$) in comparison with controls.

CONCLUSIONS

There is a significant risk of developing hypertension in cancer patients receiving vandetanib. Appropriate monitoring and treatment is strongly recommended to prevent cardiovascular complications.

Introduction

Given the heterogeneity of solid tumours and potential crosstalk between key signalling pathways, multitargeted agents represent the next generation of targeted therapies

in solid tumours [1], though targeted inhibition of a single signalling pathway, such as the vascular endothelial growth factor receptor (VEGFR) or epidermal growth factor receptor (EGFR) pathway, has been clinically validated in solid tumours, with a number of currently approved drugs

such as bevacizumab [2–6], erlotinib [7, 8] and gefitinib [9–11]. Vandetanib is a novel, orally available anticancer agent that inhibits vascular endothelial growth factor receptor-2 (VEGFR-2) and epidermal growth factor receptor (EGFR)-dependent signalling [12] as well as rearranged during transfection (RET) tyrosine kinase, which is an important growth driver in certain types of thyroid cancer [13, 14]. Clinical benefits from the administration of vandetanib in unresectable or metastatic medullary thyroid cancer (MTC) and non-small-cell lung cancer (NSCLC) have been observed in clinical trials [15–19]. In April 2011, vandetanib was approved for the treatment of patients with unresectable or metastatic MTC based on a phase III randomized controlled trial demonstrating a 54% reduction in the risk of disease progression [19, 20]. As for previously treated advanced NSCLC patients, our previous systematic review also demonstrated that vandetanib significantly improved progression-free survival [hazard ratio (HR) 0.91, 95% CI 0.83, 1.00, $P = 0.039$] and overall response rate [risk ratio (RR) 1.49, 95% CI 1.04, 2.14, $P = 0.03$] compared with standard second line treatment, including docetaxel, pemetrexed and erlotinib [21]. Moreover, the efficacy of vandetanib in other malignancies such as metastatic breast cancer, hepatocellular carcinoma, hormone-refractory prostate cancer and metastatic urothelial cancer has been investigated, though the clinical benefit from vandetanib is minimal [22–25].

Although vandetanib is well tolerated in many patients, significant toxicities are associated with its use. Fatigue, diarrhoea, acne, rash, headache, nausea, decreased appetite, abdominal pain and QT_c prolongation are the most common adverse events experienced by patients [26, 27]. Additionally, hypertension is a common side effect observed in clinical trials. In the pivotal placebo-controlled phase III trial for advanced MTC [19], 73 of 231 patients treated with vandetanib developed hypertension as compared with five of 99 patients in the control group. As for advanced NSCLC patients, treatment with vandetanib has also been associated with increased occurrence of hypertension, with its incidence ranging from 16–39% [17, 18, 28–31]. However, because of the limited number of patients in each clinical trial, the overall incidence and risk of hypertension with vandetanib is unclear. In addition, monitoring and management of hypertension is very important because poorly controlled hypertension may lead to serious cardiovascular events, dose reduction and life-threatening consequences. Therefore, we conduct this meta-analysis to investigate fully the incidence and relative risk of hypertension among patients administered vandetanib.

Methods

Search strategy

We searched Pubmed (data from 1966 to March 2012), Embase (data from 1980 to March 2012) and the Cochrane Library electronic databases. Keywords included in the

search were ‘vandetanib’, ‘ZD6474’, ‘cancer’, ‘randomized’ and ‘hypertension’. The search was restricted to clinical trials and articles published in English. Abstracts presented at the annual meetings of the American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO) (from 2001 to March 2012) were also searched manually using the same keywords. Additionally, we searched the clinical trial registration website (<http://www.ClinicalTrials.gov>) to obtain information on the registered randomized controlled trials (RCTs). We also reviewed the reference lists of the original and review articles to identify relevant studies.

Study selection

Two investigators (QWX and SZ) independently assessed the eligibility of the articles and abstracts identified by the search and discrepancies were resolved by consensus. Since the daily dose of vandetanib approved by the FDA is 300 mg day⁻¹ [19, 32], we assessed the risk of hypertension with vandetanib at this dose to ensure clinical significance. Because of the dosage variations and limited sample sizes in phase I trials, we excluded these trials from the analysis. Only phase II and III clinical trials in which only vandetanib was administered at the defined dose were included. The relevant clinical trials were manually selected carefully based on the following criteria: (i) prospective clinical trials in patients with cancer, (ii) participants assigned to treatment with only vandetanib at a dosage of 300 mg day⁻¹ and (iii) 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 between publications, only the most recent publication (and the most informative) was included.

Data extraction and quality assessment

Two independent investigators (LF and HAN) reviewed the publications and extracted the data. The following information was extracted from each included article: year of publication, treatment arm, first author’s name, number of enrolled patients, number of patients in the treatment and control groups (when available) and adverse outcomes of interest (hypertension). Available information was extracted and recorded onto a data collection form and entered into an electronic database. The quantitative 5-point Jadad scale was used to assess the quality of included trials based on the reporting of the studies’ methods and results [33]. A trial with a score of 3 or above was regarded as high quality.

Clinical endpoints

Hypertension was extracted from the safety profile in each trial. These clinical end points were recorded according to versions II or III of the Common Terminology Criteria for Adverse Events (CTCAE) of National Cancer Institute (http://ctep.cancer.gov/reporting/ctc_archive.html) [34]. Both versions describe 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 symptomatic 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 analysis was undertaken on an intention-to-treat basis. Patients were analyzed according to treatment allocated, irrespective of whether they received that treatment. 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 vandetanib 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 [35]. Between study heterogeneity was estimated

using the χ^2 -based Q statistic [36]. 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 [37, 38]. All statistical analyses were performed by using Stata version 12.0 software (Stata Corporation, College Station, Texas, USA) and Comprehensive Meta Analysis program version 2 software (Biostat, Englewood, NJ).

Results

Search results

A total of 333 potentially relevant studies were retrieved electronically, 323 of which were excluded for the reasons shown in Figure 1. Ten trials of these citations were subsequently included in the review [15, 16, 18, 19, 25, 29, 31, 39–41]. One additional conference abstract was located as a result of hand searching [42]. Finally, a total of 11 trials with 3154 patients were available for the meta-analysis. Eight trials were RCTs with a control arm [15, 18, 19, 25, 29, 31, 40, 42] and three were single arm trials [16, 39, 41].

Figure 1

Flow chart of trial selection process

Characteristics of these eligible trials are given in Table 1. For calculation of the RRs, eight trials were pooled and 1843 patients were assigned to the drug group (vandetanib 300 mg day⁻¹) and 1311 patients were assigned to the control or placebo groups. The quality of each included study was roughly assessed according to the Jadad scale and six trials had Jadad scores of 5, one trial had a Jadad score of 4, two trials had Jadad scores of 3 and two trials had Jadad scores of 2 (Table 1).

Incidence of hypertension

A total of 3154 patients with MTC, NSCLC, and other malignancies from 10 trials were included for this analysis [16, 18, 25, 29, 31, 39–42]. The incidence of hypertension ranged from 4.2 to 39.6%. The lowest incidence was noted in a phase II single arm trial among patients with metastatic breast cancer (MBC) [39] and the highest incidence was observed in patients with SCLC [40]. The meta-analysis revealed the heterogeneity of the included studies ($I^2 = 84.5\%$, $P = 0.0066$), and all the studies were included for final analysis using the random effects model. The calculated summary incidence of all grade hypertension among patients receiving vandetanib from all these trials was 24.2% (95% CI 18.1, 30.2%, Figure 2).

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 vandetanib. Eight of the 11 trials reported incidence of high grade hypertension data [15, 16, 18, 19, 29, 39–41], and the incidence of high grade hypertension ranged between 2.0 and 16.7%, with the highest incidence seen in the phase II trial by Kiura *et al.* in Japanese patients with NSCLC [41] and the lowest incidence observed in patients with MBC [39]. The calculated summary incidence of high-hypertension among 3154 patients was 6.4% (95% CI 3.3, 9.5%, Figure 3) using the random-effects model ($I^2 = 57.6\%$, $P = 0.021$).

Incidence of hypertension in patients with MTC, NSCLC and non-MTC/NSCLC tumours

In order to explore the relationship between vandetanib-associated hypertension and tumour type, we further analyzed the incidence of hypertension in patients with MTC, NSCLC and non-MTC/NSCLC tumours. Our results showed that the summary all grade and high grade incidences of hypertension in patients with non-MTC/NSCLC tumours were 15.4% (95% CI 3.2, 33.7%, sample size: 96, Table 2) and 3.4% (95% CI 1, 11.1%, sample size 77, Table 2), respectively. The incidence of all grade and high grade hypertension in non-MTC/NSCLC tumours was lower than NSCLC and MTC. Among patients with NSCLC, the pooled incidences of all grade and high grade hypertension was 21.8% (95% CI 15, 30.5%, sample size 1414, Table 2) and 7.6% (2.8–18.8%, sample size 797, Table 2), respectively. Interestingly, the incidence rate of all grade and high grade hypertension in

MTC was higher than in NSCLC and non-MTC/NSCLC tumours with a pooled all grade incidence of 32.1% (95% CI 27.3, 37.3%, sample size 333, Table 2) and high grade incidence of 8.8% (95% CI 5.9, 12.9%, sample size 261, Table 2). There was a significant difference detected between MTC and NSCLC in terms of the incidence of vandetanib-associated all grade hypertension (RR 1.48, 95% CI 1.23, 1.77, $P < 0.0001$), but not high grade hypertension (RR 1.15, 95% CI 0.73, 1.82, $P = 0.55$). Furthermore, vandetanib was associated with a significantly increased risk of all grade hypertension in comparison with non-MTC/NSCLC tumours (RR 2.06, 95% CI 1.26, 3.36, $P = 0.004$), but not high grade hypertension (RR 2.26, 95% CI 0.70, 7.33, $P = 0.17$).

Relative risk of hypertension

RR calculated from a randomized controlled trial could be used to determine specifically the contribution of vandetanib to the development of hypertension in these patients with many confounding factors such as underlying malignancy, renal function, and other therapeutic interventions. As a result, a meta-analysis of RR associated with vandetanib in comparison with controls was performed. The relevant clinical trials were manually selected carefully based on the following criteria: (i) prospective clinical trials in patients with cancer, (ii) participants assigned to treatment with only vandetanib at a dosage of 300 mg day⁻¹, (iii) events or event rate and sample size available for hypertension and (iv) the studies have a control group in the same trial. After the selection process, seven [18, 19, 25, 29, 31, 40, 42] and five RCTs [15, 18, 19, 29, 40] were included for calculating RR of all grade and high grade hypertension, respectively. The pooled RR for all grade hypertension showed that treatment of vandetanib significantly increased the risk of developing all grade hypertension in cancer patients with a RR of 5.1 (95% CI 3.76, 6.92, $P = 0.000$, Figure 4) using a fixed effects model ($I^2 = 30.0\%$, $P = 0.199$), and similar results were observed in NSCLC (RR 6.15, 95% CI 4.14, 9.12, $P = 0.000$, Figure 4), MTC (RR 4.99, 95% CI 3.76, 6.92, $P = 0.000$, Figure 4) and non-MTC/NSCLC tumours (RR 2.01, 95% CI 1.02, 3.94, $P = 0.043$, Figure 4) based on subgroup analysis. As for high grade hypertension in patients prescribed vandetanib, the combined RR also demonstrated that vandetanib was associated with a significantly increased risk of high grade hypertension among cancer patients (RR 8.06, 95% CI 3.41, 19.04, $P = 0.000$, Figure 5) using a fixed effects model ($I^2 = 25.1\%$, $P = 0.254$). Subgroup analysis also confirmed that the risk of high grade hypertension increased in NSCLC patients treated with vandetanib (RR 10.22, 95% CI 3.47, 30.1, $P = 0.000$, Figure 5). Due to only one MTC trial and one SCLC trial included in the subgroup analysis, we could not perform a combined analysis. Thus, on the whole vandetanib was associated with a significantly increased risk of all grade and high grade hypertension when compared with controls in these cancer patients.

Table 1
Baseline characteristics of the 11 included trials

Study	Phase	Underlying malignancy	Treatment arms	Number of patients	Median age (years)	Female (%)	Median PFS (months)	Median treatment (months)	Number of high grade hypertension events	Jadad score
Miller, 2005 [39]	II	MBC	Vandetanib 300 mg day ⁻¹	24	50.5	100	1.6	NR	0	2
Arnold et al. 2007 [40]	II	SCLC	Vandetanib 300 mg day ⁻¹ Placebo	53 54	56.9 62.4	49.1 42.6	2.7 2.8	1.8 3.0	2 2	5
Heymach et al. 2008 [29]	II	NSCLC	Vandetanib 300 mg day ⁻¹ Placebo +PC	73 52	63 59	33 29	2.9 5.8	NR NR	2 0	3
Kiura et al. 2008 [41]	II	NSCLC	Vandetanib 300 mg day ⁻¹	18	61	38.9	3.1	NR	3	3
Natale et al. 2009 [15]	II	NSCLC	Vandetanib 300 mg day ⁻¹ Gefitinib 250 mg day ⁻¹	83 85	63 61	42 39	2.8 2.0	NR NR	13 1	5
Wells et al. 2010 [16]	II	Advanced MTC	Vandetanib 300 mg day ⁻¹	30	49	70	27.9 weeks	18.8	3	2
Leboulleux et al. 2010 [42]	II	MTC	Vandetanib 300 mg day ⁻¹ Placebo	72 73	63	NR	11.0 5.8	18.9 19.5	24 4	4
Natale et al. 2011 [18]	III	NSCLC	Vandetanib 300 mg day ⁻¹ Erlotinib 150 mg day ⁻¹	623 617	61 61	39 36	NR NR	2.3 2.2	24 2	5
ZETA: Wells et al. 2012 [19]	III	Advanced/metastatic MTC	Vandetanib 300 mg day ⁻¹ Placebo	231 100	50.7 53.4	42 44	30.5 19.3	24 24	73 5	5
ZEPHYR:Lee et al. 2012 [31]	III	Advanced NSCLC	Vandetanib 300 mg day ⁻¹ Placebo	617 307	NA NA	NA NA	NA NA	NR NR	162 9	5
Hsu et al. 2012 [25]	II	Advanced HCC	Vandetanib 300 mg day ⁻¹ Placebo	19 23	54 56	5.3 1.3	1.05 0.95	39days 40days	2 1	5

HCC, hepatocellular carcinoma; MBC, metastatic breast cancer; MTC, medullary thyroid cancer; NA, not available; NR, not reported; NSCLC, non-small cell lung cancer; PC, paclitaxel+carboplatin; SCLC, small cell lung cancer.

Figure 2

Forest plot for meta-analysis of incidence of all grade hypertension from ten trials of patients with cancer assigned vandetanib. Weights are from random effects analysis

Publication bias

Begg's funnel plot and Egger's test were performed to assess the publication bias of the literature. The shapes of the funnel plots did not reveal any evidence of obvious asymmetry ($P = 0.881$ for all grade RR and $P = 0.602$ for high grade RR, respectively). Then, Egger's test was used to provide statistical evidence of funnel plot symmetry. The results still did not suggest any evidence of publication bias ($P = 0.247$ for all grade RR and $P = 0.077$ for high grade RR, respectively).

Discussion

Hypertension associated with angiogenesis inhibitors is a common adverse event noted in clinical trials. In addition to vandetanib, several other angiogenesis inhibitors, such as bevacizumab [43–45], sorafenib [46] and sunitinib [47], have also been associated with the development of hypertension. The association of vandetanib with hypertension may be directly related to its inhibitory effect on the VEGF

receptor. Possible mechanisms include impaired angiogenesis leading to a decrease in the density of microvessels, endothelial dysfunction associated with a decrease in nitric oxide production and an increase in oxidative stress and changes in neurohormonal factors or the renin-angiotension-aldosterone system [47, 48]. A small study by Veronese *et al.* showed that the role of neurohormonal factors in sorafenib-induced hypertension may be limited [49]. However, as yet there is a lack of data on the possible mechanism of developing vandetanib-associated hypertension. Studies focusing on this issue are required.

To the best of our knowledge, this is the first meta-analysis to investigate the overall risk of hypertension associated with vandetanib in cancer patients and to find the difference in the incidences between NSCLC, MTC and non-MTC/NSCLC tumours. Our meta-analysis results show that a high incidence of hypertension associated with vandetanib is observed in cancer patients. The majority of hypertension associated with vandetanib is grade I or II and the significance of moderate hypertension in cancer patients treated with vandetanib is less clear. Since cancer

Figure 3

Forest plot for meta-analysis of incidence of high grade hypertension from eight trials of patients with cancer assigned vandetanib. Weights are from random effects analysis

Table 2

Incidence and relative risk of hypertension with vandetanib

Groups	Incidence (95% CI)	Relative risk (95% CI)
All grade		
Overall	24.2% (18.1, 30.2)	5.10 (3.76, 6.92)
MTC	32.1% (27.3, 37.3)	4.99 (2.56, 9.74)
NSCLC	21.8% (15.0, 30.5)	6.15 (4.14, 9.12)
Non-MTC/NSCLC tumours	15.4% (3.2, 33.7)	2.01 (1.02, 3.94)
High grade		
Overall	6.4% (3.3, 9.5)	8.06 (3.41, 19.04)
MTC	8.8% (5.9, 12.9)	NA
NSCLC	7.6% (2.8, 18.8)	10.22 (3.47, 30.11)
Non- MTC/NSCLC tumours	3.4% (1, 11.1)	NA

MTC, medullary thyroid cancer; NA, not available; NSCLC, non-small cell lung cancer.

patients are surviving longer, improving the quality of life by reducing complications is an important issue. It is accepted that hypertension is an independent risk factor for both renal and cardiovascular events [50, 51]. Therefore,

it is important that mild to moderate hypertension induced by vandetanib should be recognized and managed appropriately. Severe hypertension is not infrequent with the use of vandetanib, but the significance of severe hypertension is evident because of its cardiovascular complications.

The risk of hypertension may vary substantially with tumour type. Thus we performed a sub-group analysis based on tumour types. Our results showed that the summary all grade and high grade incidences of hypertension in patients with non-MTC/NSCLC tumours was lower than NSCLC and MTC, while the incidence rate of all grade and high grade hypertension in MTC was higher than other kinds of tumours. The variability in the incidence of all grade and high grade hypertension in the different cancer types may be due to variations in treatment duration. The median treatment period for a non-thyroid malignancy ranges from 1.3 to 3.0 months. However, the median duration of thyroid cancer therapy ranges from 18.8 to 24 months. Further exploratory analyses found that vandetanib was associated with a significantly increased risk of all grade hypertension in comparison with NSCLC and

Figure 4

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

non-MTC/NSCLC tumours. Thus, clinicians and patients need to know that there are different risks for different diseases.

The management of vandetanib-associated hypertension is still under debate. According to the manufacturer package insert for vandetanib, all patients receiving vandetanib should be monitored for hypertension and it should be controlled as appropriate. In cases of severe or persistent hypertension despite the initiation of antihypertensive treatment, dose reduction or interruption may be necessary. If patients with high blood pressure cannot be controlled, vandetanib should not be restarted [27]. In most patients, hypertension can be controlled with standard antihypertensive medications. However, the biological effect of these antihypertensive medications on angiogenesis and its implications should be considered, and need to be fully understood. Both enalapril (an angiotensin-converting enzyme [ACE] inhibitor) and candesartan (an

angiotensin II receptor antagonist) can specifically inhibit VEGF induced myocardial angiogenesis in the normal heart [52]. In addition, Wu *et al.*'s study also confirmed that candesartan could significantly suppress VEGF expression and show an antiangiogenesis effect in a xenograft model of bladder cancer [53]. However, Miura *et al.* found that nifedipine (a calcium channel blocker) could induce VEGF secretion from coronary smooth muscle cells [54]. As a result, the possibility exists that some antihypertensive medications are more effective in treating anti-VEGF-associated hypertension and have less toxic effects when used in conjunction with vandetanib.

One of the strengths of the present meta-analysis is that we quantitatively identified the incidence of hypertension by using data from trials of patients who had undergone vandetanib therapy for different cancers. Clinical benefits from the administration of vandetanib in MTC and other type of tumours have been observed in clinical

Figure 5

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

trials. As a result, it is worthwhile to devote resources toward a detailed evaluation of its adverse effects because it might be widely used in clinical practice. Besides, a detailed analysis of the adverse effects would be warranted if the information on potential harm appears to be essential for guiding the decisions of clinicians, consumers, and policymakers. Many of the RCTs in our study have extremely few patients so that the data are not reliable for detecting meaningful differences in the incidence of adverse events. However, this meta-analysis combines data from a number of trials and thus has greater statistical reliability. Moreover, no evidence of publication bias has been found, but our meta-analysis is still far from perfect. Some limitations need to be carefully considered when interpreting the results. First, our findings are clearly affected by the limitations of the individual clinical trials included in the analysis [46]. (i) These trials may have underestimated the incidence of vandetanib-associated hypertension because of imperfections of the CTCAE

version 2 or 3 for recording adverse events [34]. In both these versions, patients are considered hypertensive only if diastolic pressure is increased by more than 20 mm Hg or blood pressure is greater than 150/100 mm Hg. In our study, this grading criteria would have missed many patients with hypertension according to the standard criteria for the diagnosis of hypertension (140/90 mmHg). (ii) The grading criteria do not clearly differentiate between grade 2 and 3 hypertension, and our findings of high grade hypertension could be affected by the overlap between these two grades. (iii) Baseline hypertension of the patients was not described in the trials included in our meta-analysis, which may have led to an overestimation of the incidence of vandetanib induced hypertension. Second, we only assessed the incidence and risk of hypertension with vandetanib (300 mg day⁻¹) in this study. The risk at other doses or in combination with other anticancer drugs is not evaluated. Thirdly, although our findings show that patients with MTC have a higher incidence of all grade and

high grade hypertension, this finding may be limited by the small sample size of MTC patients. Finally, it was not an individual patient data analysis, and therefore, it precludes a more comprehensive analysis, such as adjusting for baseline factors and other differences that exist between the trials from which the data are pooled.

In conclusion, despite the limitations of our meta-analysis, we conclude that vandetanib is associated with a significantly increased risk of developing hypertension. Early detection and effective management of hypertension might allow for safer use of this drug. And further studies will be needed to identify the mechanism of vandetanib-associated hypertension.

W.X.Q., L.N.T. and S.Z. took part in the literature review, data extraction and analysis and writing of the manuscript. A.N.H. and F.L. took part in the literature search, statistical analyses and wrote the first draft of the original manuscript. W.X.Q., D.L.M. and Y.J.S. took part in conceptualization and writing the manuscript. Y.Y. took part in conceptualization, data analysis and interpretation and provided scientific advice. All authors contributed to the revision of the manuscript. The views expressed in this review are the opinions of the authors. All authors had full access to all the data in the study. Q.W.X. and Y.Y. take responsibility for the integrity of the data and the accuracy of the data analysis.

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 Z.S. had support from the National Natural Science Foundation of China (81172105) and Science and Technology Commission of Shanghai (09140902200) for the submitted work, A.N.H. had support from the National Natural Science Foundation of China (81001191) and Science and Technology Commission of Shanghai (10PJ1408300) 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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