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Risk of arterial thromboembolic events with vascular endothelial growth factor receptor tyrosine kinase inhibitors: An up-to-date meta-analysis

Wei-Xiang Qi *, Zan Shen, Li-Na Tang, Yang Yao

Department of Oncology, Shanghai Jiao Tong University affiliated Sixth People's Hospital, No. 600, Yishan Road, Shanghai 200233, China

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Contents

Abstract

Purpose: Arterial thromboembolic events (ATEs) with vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR–TKIs) have emerged as a serious concern, we perform a meta-analysis of randomized controlled trials (RCTs) to determine the incidence and risk of ATEs in cancer patients treated with these agents.

Methods: The databases of PubMed and Web of Science were searched for relevant articles. Statistical analyses were conducted to calculate the summary incidence, odds ratio (OR), and 95% confidence intervals (CIs) by using either random effects or fixed effect models according to the heterogeneity of included studies.

Results: A total of 9711 patients from 19 RCTs were included. The overall incidence of ATEs was 1.5% (95%CI: 1.0–2.3%). The use of VEGFR–TKIs significantly increased the risk of developing ATEs when compared with controls (OR 2.26, 95%CI: 1.38–3.68, $p = 0.001$). Sensitivity analysis indicated that the significance estimate of pooled ORs was not significantly influenced by omitting any single study. In subgroup analyses, the odds ratio of ATEs did not significantly vary with tumor types ($p = 0.70$), VEGFR–TKIs ($p = 0.32$), treatment regimens ($p = 0.76$), phase of trials ($p = 0.37$) and sample size ($p = 0.89$). Additionally, the most common events for ATEs were cardiac ischemia/infarction (67.4%), CNS ischemia (7.9%) and cerebrovascular accident (6.7%).

* Corresponding author. Tel.: +86 021 64369181 58430; fax: +86 021 64701361.
E-mail addresses: qiweixiang1113@163.com, qiweixiang@live.cn (W.-X. Qi).

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Conclusion: In this largest meta-analysis to date, we find that treatment with VEGFR–TKIs significantly increase the risk of developing ATEs. Further studies are still needed to investigate this association. In the appropriate clinical scenario, the use of these drugs remains justified in their approved indications.

Keywords: Arterial thromboembolic events; VEGFR–TKIs; Angiogenesis inhibitors; Meta-analysis

1. Introduction

Recent advances in the understanding of the pathogenesis of cancer have led to the introduction of a variety of biological agents with novel mechanisms of action into clinical trials and even into clinical practice. One such therapeutic target is the vascular endothelial growth factor (VEGF) pathway, a critical mediator of tumor angiogenesis [1,2]. In the last decade, several small-molecule tyrosine kinase inhibitor (TKIs) and monoclonal antibody, mainly targeting vascular endothelial growth factor receptor (VEGFR), have been developed and currently under evaluation for activity in a variety of solid tumors. At present, the United States Food and Drug Administration (FDA) has approved six VEGFR–TKIs for use in cancer therapy–sunitinib (Sutent, Pfizer, New York, NY) [3–5], sorafenib (Nexavar, Bayer Pharmaceuticals, West Haven, CT, and Onyx Pharmaceuticals, Richmond, CA) [6,7], pazopanib (Votrient, GlaxoSmithKline, Middlesex, UK) [8,9], vandetanib (Caprelsa, AstraZeneca, London, UK) [10], axitinib (Inlyta, Pfizer, New York, NY) [11,12] and regorafenib (BY 73-4506, Bayer Schering Pharma AG, Berlin, Germany) [13].

Although VEGF-targeted agents lack the typical adverse effects of cytotoxic chemotherapy agents, these drugs exhibit unique toxicities including an increase risk of developing hypertension [14–20], hand–foot skin reaction [21–25], bleeding [26–28], and gastrointestinal perforation [29,30]. Arterial thromboembolic events (ATEs) are a rare but potentially life-threatening events associated with VEGF-targeted agents. Several previous meta-analyses showed that the addition of bevacizumab to chemotherapy, a humanized anti-VEGF monoclonal antibody, significantly increased the risk of ATE when compared to chemotherapy alone [31–33]. While another meta-analysis also demonstrated that the use of sunitinib and sorafenib significantly increased the risk of ATEs when compared to controls (RR, 3.03, 95%CI: 1.25–7.37; $p = 0.015$) [34], but that report is limited by a small number of randomized controlled trials (RCTs) (only three trials) included for analysis. As a result, the pooled results might be affected by a single large RCT. Also, ATEs includes the involvement of several different arteries such as such as coronary artery and cerebral artery, questions remain regarding the effect of VEGFR–TKIs on the risk of specific type of ATEs such as cardiac ischemia, myocardial infarction or cerebrovascular accident. In addition, several newly developed VEGFR–TKIs share a similar spectrum of target receptors with sunitinib and sorafenib might be also associated with increased risk of developing ATEs. Indeed, ATEs related to these drugs have been sporadically reported in recent clinical trials [35–39]. Therefore, we conduct a meta-analysis of all RCTs to determine whether the use of VEGFR–TKIs increase the risk of ATEs in cancer patients.

2. Methods

2.1. Data sources

We conducted an independent review of citations from PubMed between January 1, 1966 and October 31, 2013. Key words were sorafenib, nexavar, BAY43-9006, sunitinib, sutent, SU11248, pazopanib, votrient, GW786034, vandetanib, caprelsa, ZD6474, axitinib, cediranib, tivozanib, regorafenib, cabozantinib, brivanib, randomized controlled trials and cancer. The search was limited to prospective RCTs published in English. The search strategy also used text terms such as angiogenesis inhibitors and vascular endothelial growth factor receptor-tyrosine kinase inhibitors to identify relevant information. We also performed independent searches using Web of Science databases between January 1, 1966 and October 31, 2013, to ensure that no clinical trials were overlooked. Additionally, we searched the clinical trial registration website (http://www.ClinicalTrials.gov) to obtain information on the registered prospective trials. We also searched abstracts and virtual meeting presentations from the American Society of Clinical Oncology (http://www.asco.org/ASCO) conferences that took place between January 2004 and January 2013. Reference lists from relevant primary studies and review articles were also examined to find additional publications. Each publication was reviewed and in cases of duplicate publication only the most complete, recent, and updated report of the clinical trial was included in the meta-analysis.

Study selection was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [40]. Clinical trials that met the following criteria were included: (1) prospective randomized controlled phase II and III trials; (2) participants assigned to treatment with VEGFR–TKIs (alone or in combination at any dosage or frequency); and (3) available data regarding events or incidence of ATEs and sample size. Phase I trials were excluded because of inter study variability in drug dosing as well as the small number of patients in these trials.