Cancer Treatment Reviews 53 (2017) 120–127

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Systematic or Meta-analysis Studies

Cardiovascular toxicity of angiogenesis inhibitors in treatment of malignancy: A systematic review and meta-analysis

Husam Abdel-Qadir [a,b,c,d,*], Josee-Lyne Ethier [a,e], Douglas S. Lee [a,b,c,f], Paaladinesh Thavendiranathan [a,f], Eitan Amir [a,c,e]

[a] Department of Medicine, University of Toronto, Toronto, Ontario, Canada
[b] Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada
[c] Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada
[d] Women's College Hospital, Toronto, Ontario, Canada
[e] Princess Margaret Cancer Centre, Toronto, Ontario, Canada
[f] Peter Munk Cardiac Centre and Joint Department of Medical Imaging, University Health Network, Toronto, Ontario, Canada

ARTICLE INFO

Article history:
Received 21 October 2016
Received in revised form 8 December 2016
Accepted 9 December 2016

Keywords:
Antineoplastic agents/adverse effects
Angiogenesis inhibitors
Cardiotoxins
Vascular endothelial growth factor
Bevacizumab
Sorafenib
Sunitinib
Vandetanib
Aflibercept

ABSTRACT

Background: The cardiovascular risk of angiogenesis inhibitors is not well-quantified. We hypothesized that, compared to direct vascular endothelial growth factor (VEGF) inhibitors (anti-VEGF antibodies or decoy receptors), small molecule agents have higher risk due to their less specific mechanism.
Methods: We searched the MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials for phase III randomised controlled trials comparing angiogenesis inhibitor-based therapy to other systemic therapy. Outcomes evaluated were hypertension, severe hypertension, cardiac dysfunction, congestive heart failure, cardiac ischemia, arterial thromboembolism, venous thromboembolism, and fatal cardiovascular events. Data were pooled using Mantel-Haenszel random effects method to generate odds ratios (OR).
Results: We identified 77 studies meeting inclusion criteria. Compared to routine care, angiogenesis inhibitors were associated with a higher risk of hypertension (OR 5.28 [4.53–6.15], number needed to harm [NNH] 6), severe hypertension (OR 5.59 [4.67–6.69], NNH 17), cardiac ischemia (OR 2.83 [1.72–4.65], NNH 85) and cardiac dysfunction (OR 1.35 [1.06–1.70], NNH 139). VEGF inhibitors were associated with an increased risk of arterial thromboembolism (OR 1.52 [1.17–1.98], NNH 141). No significant interaction was observed between the two drug subgroups for any outcomes. We identified no significant increase in the risk of the other outcomes evaluated.
Conclusion: Angiogenesis inhibitors increase the risk of hypertension, arterial thromboembolism, cardiac ischemia and cardiac dysfunction. There was no significant difference in cardiovascular risk between direct VEGF inhibitors and small molecule agents.

Introduction

Angiogenesis is a key factor for tumor growth and survival [1,2]. Accordingly, angiogenesis inhibition is an attractive target for suppressing tumor growth, and angiogenesis inhibitors have been shown to improve outcomes in a variety of malignancies. Most angiogenesis inhibitors exert their effect by inhibiting the vascular endothelial growth factor (VEGF) signalling pathway, via one of two mechanisms [3,4]. The first is direct inhibition of the VEGF ligand's ability to bind to its target receptor. The monoclonal antibodies, bevacizumab [5] and ramucirumab [6], as well as the VEGF decoy receptor aflibercept [7] inhibit angiogenesis via this mechanism. The second class of angiogenesis inhibitors are small molecules that inhibit the tyrosine kinases which would be activated by the VEGF ligand-receptor interaction. Agents in this class include sunitinib [8], sorafenib [9], pazopanib [10], vandetanib [11], vatalanib [12], cabozantinib [13], axitinib [14], and regorafenib [15] amongst others. In contrast to monoclonal antibodies, small molecules typically target multiple tyrosine kinases other than VEGF.

The inhibition of VEGF has deleterious effects on the cardiovascular system [3,4]. VEGF inhibitors have been associated with an increased risk of adverse cardiovascular events such as hyperten-

* Corresponding author at: 4th Floor, Cardiology Clinic, Women's College Hospital, 76 Grenville Street, Toronto, Ontario M5S1B2, Canada. Fax: +1 800 953 0138.
E-mail address: h.abdel.qadir@mail.utoronto.ca (H. Abdel-Qadir).

http://dx.doi.org/10.1016/j.ctrv.2016.12.002
0305-7372/

sion, thromboembolic events, myocardial ischemia, left ventricular dysfunction, heart failure, and QT interval prolongation (with possible associated arrhythmias). However, these are rare events among patients enrolled in clinical trials, and individual studies designed to demonstrate efficacy of each of these agents are underpowered to detect statistically significant differences in the incidence of adverse cardiovascular events other than common toxicities such as hypertension. Moreover, it is unclear if the mechanistic differences between the two classes translate into clinically relevant differences in the rate of these cardiovascular events. Finally, it has been difficult to quantify how many of these adverse events lead to death, which is an important consideration in patients who are being treated with these drugs for advanced malignancies that pose an important competing risk of death. To determine the risk of adverse cardiovascular events associated with these agents, we conducted a systematic review of phase III and IV randomized controlled trials of adult patients with malignancy treated with routine care with or without an angiogenesis inhibitor.

Methods

Search strategy

We conducted a systematic review and meta-analysis of Phase III randomised controlled trials (RCTs) and phase IV post-marketing studies according to PRISMA guidelines [16]. The main comparison was standard therapy, as determined by individual studies for the given malignancy being treated, compared with standard therapy plus an angiogenesis inhibitor. The angiogenesis inhibitors considered were: bevacizumab, aflibercept, ramucirumab, sunitinib, sorafenib, pazopanib, vandetanib, cabozantinib, axitinib, ponatinib, and regorafenib. Inclusion was not restricted based on language of publication. The studies were limited to those assessing patients aged 18 years or above, who are being treated for malignancy (solid or hematologic) at the time of study enrollment.

The MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) databases was searched with the aid of a librarian in June 2014 to identify all eligible studies published after 1990. The search was done in accordance with PRISMA recommendations. The search strategy combined three concepts: (1) malignancy; (2) angiogenesis inhibitors (individual drug names, as well as Medical Subject Heading related to Angiogenesis inhibitors, tyrosine kinase inhibitors, and VEGF), and (3) phase III/IV RCTs. To increase sensitivity, the search strategy did not include terms for cardiovascular or adverse events. The detailed search strategy is provided in Appendix 1.

Data extraction and management

The citations obtained from the electronic search were initially de-duplicated by the librarian conducting the search, and were subsequently manually de-duplicated by one author (HAQ) who then reviewed the titles and abstracts to select papers for more detailed review. Studies were reviewed independently by HAQ and JLE and data extracted independently using a common data abstraction form in Microsoft Excel [17]. Disagreements between the two reviewers were resolved by consensus, or by deference to a third author (EA) if needed. Reasons for exclusion were documented. If there were multiple reports of the same trial, we included data from the most up-to-date reference possible.

The outcomes of interest were: (1) hypertension; (2) severe hypertension (Grade 3 or higher); (3) arterial thromboembolic events; (4) cardiac dysfunction; (5) congestive heart failure; (6) cardiac ischemia and (7) fatal cardiovascular events. For all outcomes, we used the definition of the adverse event used by the individual clinical trials. We also initially aimed to include venous thromboembolism as an eighth outcome. Due to variable outcome definitions within trials, we assessed the following related outcomes: (1) deep vein thrombosis (DVT); (2) pulmonary embolism (PE); (3) VTE with site unspecified; (4) unspecified thromboembolism. At study onset, we had planned to study QT prolongation and arrhythmias as an additional outcome but this was rarely reported and this objective was thus abandoned.

The number of patients in each treatment arm who experienced the outcome of interest and the number of patients in the safety analysis were extracted from each study. Data were extracted from intention-to-treat analyses wherever possible. In cases where there were multiple intervention groups, we assessed the ones that were deemed closest to our primary intention of comparing background therapy without an angiogenesis inhibitor to the same therapy with the addition of the agent of interest. If there were arms that exposed patients to different doses of an angiogenesis inhibitor, those arms were pooled together. We also aimed to collect data on the weighted average of the median follow-up duration for adverse events in the study arms (or the mean if the median was unavailable). This was often not explicitly stated. Accordingly, we collected data on treatment duration, or when that was unavailable, progression-free survival as a surrogate. If none of these data were reported, we collected median follow-up instead. The risk of bias for each study was assessed using a modified version of the Cochrane Risk of Bias tool [18] that was modified to take into account funding by the pharmaceutical industry.

Data synthesis and statistical analysis

The extracted data were transferred to the Review Manager (RevMan) software package, Version 5.3 [19]. The event numbers and numbers at risk were used to generate an odds ratio for the adverse cardiovascular outcome of interest in angiogenesis – inhibitor-treated patients compared to those who were not. It was anticipated that event rates would be low with frequent zero events within study arms. Thus, the Mantel-Haenszel random effects model with zero-cell corrections was used to pool the results for the purposes of this report. A random effects model was chosen to account for heterogeneity in included patients, underlying malignancies, and treatment regimens. Funnel plots for adverse outcomes were inspected visually for subjective evidence of substantial publication bias.

We performed subgroup analyses comparing VEGF ligand/receptor inhibitors (typically monoclonal antibodies or decoy receptors) with small-molecule tyrosine kinase inhibitors. We also performed subgroup analyses based on whether treatment was delivered in the adjuvant or palliative setting, and study blinding status. We studied if the risk of heart failure, cardiac dysfunction, and fatal cardiovascular events was affected by concurrent anthracycline exposure as part of the standard treatment. In addition, we performed meta-regression analyses using linear regression weighted by study sample size to explore the influence of mean/-median age and sex (the proportion of women in individual studies) on the OR for each outcome of interest. Differences between subgroups were assessed using methods described by Deeks et al. [20]. Absolute risks of each adverse event were calculated as the number of events per person over the follow-up period of the trial. The difference in absolute risk between the angiogenesis inhibitor group and the control group was also presented as the number needed to harm (NNH). All statistical tests were two-sided, and statistical significance was defined as $P < 0.05$.