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Critical Reviews in Oncology/Hematology 92 (2014) 194–207

CRITICAL REVIEWS IN
Oncology
Hematology
Incorporating Geriatric Oncology

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Risk of cardiovascular toxicities in patients with solid tumors treated with sunitinib, axitinib, cediranib or regorafenib: An updated systematic review and comparative meta-analysis

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Accepted 23 June 2014

Contents

Abstract

Background: We performed a systematic review and comparative meta-analysis of cardiovascular toxicities associated with sunitinib, axitinib, cediranib or regorafenib; oral multi tyrosine kinase inhibitors.
Patients and methods: Eligible studies included randomized phase II and III trials of patients with solid tumors on sunitinib, axitinib, cediranib or regorafenib describing daily events of hypertension, left ventricular dysfunction, bleeding or thrombosis.
Results: Patients treated with these four agents had a significantly increased risk of all-grade hypertension and bleeding. The RR of all-grade hypertension, bleeding, thrombosis and cardiac dysfunction were 2.78 (95% CI 2.03–3.81; $p < 0.00001$), 1.93 (95% CI 1.41–2.64; $p < 0.00001$),

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http://dx.doi.org/10.1016/j.critrevonc.2014.06.003
1040-8428/

0.85 (95% CI 0.60–1.19; $p = 0.50$), 2.36 (95% CI 0.95–5.87; $p = 0.06$), respectively. Exploratory subgroup analysis showed no effect of the agent used (sunitinib vs. axitinib vs. cediranib) in the risk of hypertension; while for bleeding, only the sunitinib subgroup RR was significant compared to axitinib or cediranib.

Conclusions: Our meta-analysis has demonstrated that sunitinib, axitinib, cediranib and regorafenib are associated with a higher risk of developing all grade and high grade hypertension compared with control. While for bleeding, only the sunitinib subgroup RR was significant compared to axitinib or cediranib. Clinicians should be aware of these risks and perform regular cardiovascular monitoring.

Keywords: Sunitinib; Meta-analysis; Cardiovascular toxicities; Hypertension; Left ventricular dysfunction

1. Introduction

Sunitinib, axitinib, cediranib and regorafenib; are a group of multi-targeted receptor tyrosine kinase inhibitors with effects on cell proliferation and angiogenesis. They are potent inhibitors of platelet-derived endothial growth factor receptors (PDGFR-a and β), vascular endothelial growth factor receptors (VEGFR-1, 2 and 3), stem cell factor receptor (KIT) and Fms-like tyrosine kinase-3 (FLT3) [1,2].

Currently, the United States Food and Drug Administration (FDA) has approved sunitinib for patients metastatic renal cell carcinoma, pancreatic neuroendocrine tumors and refractory gastrointestinal stromal tumors (GIST). While axitinib has been approved for patients with metastaic renal cell carcinoma and regorafenib for metastatic colorectal carcinoma [3,4,12].

The use of these agents has been accompanied by a unique spectrum of adverse events, which are different from traditional cytotoxic anticancer therapies. For instance, previous studies have shown an increased risk of all-grade rash, all-grade stomatitis, and some metabolic complications including thyroid and liver dysfunction [3–5,11,13]. Additionally, cardiovascular toxicities associated with these agents like hypertension, left ventricular dysfunction, bleeding or thrombosis have been reported in randomized controlled trials. However, there has been a substantial variation in the incidence among clinical trials. There has been no systematic attempt to synthesize these data and the overall risk of cardiovascular toxicities induced by these agents has yet to be defined. Therefore, we conducted a systematic review and comparative meta-analysis of available clinical trials to determine the overall risk of developing cardiovascular toxicities in patients treated with this group of agents.

2. Methods

2.1. Data source

We conducted an independent review of Medline databases from January 1966 to September 2013 using "sunitinib, axitinib, cediranib or regorafenib" as search keywords. The search was limited to human, cancer, and randomized clinical trials published in English. We manually searched abstracts and presentations containing the same search terms from the American Society of Clinical Oncology (ASCO) conferences held between January 2006 and January 2013 to search for relevant trials. An independent search of the Google scholar and Cochrane electronic databases was also performed to ensure that no additional clinical trials had been overlooked. In cases of duplicate publications, only the most complete, recent, and updated report of the clinical trial was included. Finally, the most updated package inserts of the four agents were reviewed to identify relevant information [6]. Trials were selected and systemically reviewed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [7].

2.2. Study selection

Clinical trials that met the following criteria were included:

(1) Randomized controlled phase II and III trials in patients with solid tumors.
(2) Participants assigned to treatment with one of the four agents daily.
(3) Events or event rate and sample size available for all-grade cardiovascular toxicities including hypertension, left ventricular dysfunction, bleeding or thrombosis.

For incidence analysis and relative risk analysis, we included trials that randomly assigned participants to either one of these agents vs. placebo or control drug in addition to the same treatment. Phase I trials were excluded because of the different drug dosages as well as the small number of patients in these trials. Meeting abstracts without subsequent full text publication were also excluded. Independent reviewers (O.A. and M.F.) screened reports that included the key term by their titles and abstracts for relevance. Then, full texts of the relevant articles were retrieved to assess eligibility. The references of relevant reports were also reviewed manually.

2.3. Data extraction and clinical end points

Two investigators (O.A and M.F) independently performed data extraction. The following information was recorded for each study: first author's name, year of