Critical Reviews in Oncology/Hematology 102 (2016) 89–100

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Risk of cardiovascular adverse events in patients with solid tumors treated with ramucirumab: A meta analysis and summary of other VEGF targeted agents

Omar Abdel-Rahman *, Hesham ElHalawani

Clinical Oncology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt

Contents

ARTICLE INFO

Article history:
Received 1 April 2015
Received in revised form 7 April 2016
Accepted 11 April 2016

Keywords:
Ramucirumab
Hypertension
Bleeding
Thrombosis

ABSTRACT

Background: We performed a systematic review and meta-analysis of the risk of cardiovascular adverse events associated with ramucirumab.
Patients and methods: Eligible studies included randomized phase II and III trials of patients with solid tumors on ramucirumab; describing events of hypertension, bleeding, arterial/venous thrombosis and congestive heart failure.
Results: Our search strategy yielded 160 potentially relevant citations from Pubmed/Medline, CENTRAL Cochrane registry and ASCO meeting library. After exclusion of ineligible studies, a total of 11 clinical trials were considered eligible for the meta-analysis. The RR of all-grade hypertension, bleeding, ATE, VTE and congestive heart failure were 2.83 (95% CI 2.43–3.29; $p < 0.0001$), 1.98 (95% CI 1.77–2.21; $p < 0.0001$); 0.97 (95% CI 0.62–1.52; $p = 0.91$), 0.83 (95% CI 0.52–1.35; $p = 0.46$), 1.36 (95% CI 0.77-2.4; $p = 0.28$), respectively.
Conclusions: Our meta-analysis has demonstrated that ramucirumab is associated with an increased risk of hypertension and bleeding. Clinicians should be aware of this risk and perform regular clinical monitoring.

* Corresponding author at: Clinical Oncology Department, Faculty of Medicine, Ain Shams University, Lotfy Elsayed street, 11665 Cairo, Egypt.
E-mail address: omar.abdelrhman@med.asu.edu.eg (O. Abdel-Rahman).

http://dx.doi.org/10.1016/j.critrevonc.2016.04.003
1040-8428/

1. Introduction

Ramucirumab is a new vascular endothelial growth factor receptor-2 (VEGFR-2) directed monoclonal antibody that has received considerable momentum and attention in the management of numerous solid tumors (Fontanella et al., 2014). Following the initial publication of 2 landmark phase III studies in second line management of advanced gastric/gastroesophageal cancers, it has received FDA approval for this indication both alone and in combination with paclitaxel (Wilke et al., 2014; Fuchs et al., 2014). Subsequently, positive results have been released for ramucirumab in the treatment of other solid tumors including metastatic colorectal cancer (mCRC) and advanced non small cell lung cancer (NSCLC) and it has been approved for both diseases (Mackey et al., 2014; Tabernero et al., 2015a).

Ramucirumab—like other VEGF pathway targeted agents- has been linked to a characteristic variety of adverse events, which is different from traditional cytotoxic therapies (Abdel-Rahman, 2015). For example, multiple studies have suggested an increased risk of gastrointestinal, hepatobiliary as well as cardiovascular events with the use of ramucirumab (Abdel-Rahman and ElHalawani, 2014, 2015a,b). However, there has been a substantial variation in the incidence of cardiovascular adverse events among clinical trials. Additionally, there has been no comprehensive systematic attempt to synthesize these data and the overall risk of cardiovascular toxicities induced by ramucirumab needs to be further clarified particularly with the publication of new randomized studies.

2. Objective of the meta analysis

We conducted a systematic review and meta-analysis of available clinical trials to determine the overall risk of cardiovascular adverse events in solid tumor patients treated with ramucirumab.

3. Methods

3.1. Data source

We conducted a literature review of Pubmed, Cochrane and Google Scholar databases from February 1966 to March 2015 using "ramucirumab" as search keywords. The search was limited to randomized clinical trials involving human solid tumors patients published in English. We also searched abstracts and presentations containing the same search term from the American Society of Clinical Oncology (ASCO) and European society of medical oncology (ESMO) conferences. Trials were selected and systemically reviewed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009).

3.2. Study selection

Clinical trials that fulfill the following criteria were included:

(1) Randomized controlled trials in patients with solid tumors.
(2) Participants were allocated to treatment with ramucirumab-based treatment vs. control.
(3) Events and sample size available for all-grade and high grade hypertension, bleeding, arterial thromboembolic events (ATE), venous thromboembolic events (VTE) and congestive heart failure.

*ATE include: coronary ischemia, limb ischemia, intestinal ischemia and cerebrovascular ischemia.

*VTE include: deep venous thrombosis and pulmonary embolism.

For incidence analysis and relative risk analysis, we included trials that randomly assigned participants to either ramucirumab-based treatment vs. placebo or control treatment.

3.2.1. Exclusion criteria

(1) Meeting abstracts without subsequent full text publication were excluded.
(2) Phase I studies were also excluded because of concerns about different dose ranges used.

Independent reviewers (O.A. and H.E.) screened reports that included the key term by their titles and abstracts for relevance. Then, full texts of the relevant articles were examined to assess eligibility.

3.3. Data extraction and clinical end points

Two investigators (O.A and H.E.) independently conducted data extraction. The following information was recorded for each study: first author's name, year of publication, trial phase, underlying cancer, treatment regimens and arms, number of patients available for analysis, number of events of relevant adverse events.

Any discrepancies between review authors were resolved by consensus. The number of patients evaluable for toxicity was utilized as the number analyzed for each study. In the included clinical trials, cardiovacular adverse events were recorded according to the common toxicity criteria of adverse events (CTCAE) version 3.0 or 4.0, which are quite similar in terms of grading the relevant adverse events.

3.4. Statistical analysis

The principal summary measures were relative risk (RR) and corresponding 95% CIs of all grade (grade 1–4) cardiovascular toxicities. For all calculations of RRs and CIs, we have used data extracted only from randomized controlled studies, comparing the incidence of each adverse event in patients assigned to ramucirumab-based regimen with those assigned to control treatment in the same trial. To calculate 95% CIs, the variance of a log-transformed study-specific RR was derived using the delta method. Statistical heterogeneity in results between studies included in the meta-analysis was assessed through Cochrane's Q statistic, and inconsistency was quantified through I2 statistic, which estimates the percentage of total variation across studies due to heterogeneity rather than chance. The assumption of homogeneity was considered invalid for p values less than 0.10. RRs were calculated using random- or fixed-effects models depending on the heterogeneity of included studies. When substantial heterogeneity was not found, the pooled estimate calculated based on the fixed-effects model was reported by using inverse variance method. When substantial heterogeneity was found, the pooled estimate calculated based on the random-effects model was reported through using the DerSimonian method, which considers both within-study and between-study variations (DerSimonian and Laird, 1986; Higgins et al., 2003). Statistical analyses were performed by using the program Review Manager 5.3 (Copenhagen, Denmark).

4. Results

4.1. Search results

- Our search strategy yielded 160 potentially relevant citations on ramucirumab from Pubmed/Medline, CENTRAL Cochrane reg-