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Risk of gastrointestinal perforation in cancer patients treated with vascular endothelial growth factor receptor tyrosine kinase inhibitors: A systematic review and meta-analysis

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Contents

Abstracts

Background: The use of vascular-endothelial growth factor (VEGF) antibody bevacizumab is associated with an increased risk of gastrointestinal (GI) perforation, but the incidence and risk of GI perforation associated with vascular endothelial growth factor tyrosine-kinase inhibitors (VEGFR-TKIs) has not been well described. We conduct a systematic review and meta-analysis of published trials to evaluate the overall incidence and risk of GI perforation associated with VEGFR-TKIs.

Methods: Databases from PubMed, Web of Science and abstracts presented at ASCO meeting up to March 31, 2013 were searched to identify relevant studies. Eligible studies included prospective phase II and III trials evaluating VEGFR-TKIs in cancer patients with adequate data on GI perforation. 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 5352 patients with a variety of solid tumors from 20 clinical trials were included in our analysis. The incidence of GI perforation was 1.3% (95%CI: 0.8–2.0%) among patients receiving VEGFR-TKIs, with a mortality of 28.6% (15.0–47.6%). Patients treated

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with VEGFR-TKIs did not significantly increase the risk of GI perforation compared with patients treated with control medication, with an OR of 2.99 (95%CI: 0.85–10.53, $p = 0.089$). Sub-group analysis showed that the incidence of GI perforation did not significantly vary with tumor types, VEGFR-TKIs and treatments regimens. No evidence of publication bias was observed.

Conclusions: The use of VEGFR-TKIs dose not significantly increase the risk of GI perforation in comparison with the controls. Further studies are recommended to investigate this association and the risk differences among different tumor types, VEGFR-TKIs or treatment regimens.

Keywords: Cancer; Gastrointestinal perforation; Sorafenib; Sunitinib; Vandetanib; Axitinib; Pazopanib; Cediranib; Meta-analysis

1. Introduction

Angiogenesis plays a pivotal role in tumor growth, progression, and metastasis, thus the tumor vasculature is a good target for therapy [1–4]. Vascular endothelial growth factor (VEGF), a potent angiogenic factor, is over-expressed in many human tumors, and its overexpression is associated with tumor progression and poor prognosis [5]. Additionally, unlike tumor vessels that have VEGF as survival factor, the normal adult vasculature is regarded as largely independent of VEGF for survival, stability and normal function. As a result, inhibition of VEGF represents a promising therapeutic approach for cancer treatment [6,7]. In deed, therapies that inhibit the VEGF pathway, including VEGF monoclonal antibody bevacizumab and vascular epithelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKIs), have shown clinical efficacy in the treatment of many types of malignancies and have been approved for use in cancer therapy by regulatory agencies [8–18].

The toxicity profiles resulting from VEGF pathways inhibitors are unique and different from traditional cytotoxic chemotherapeutic agents. For instance, previous studies had demonstrated an increased risk of developing hypertension, hand-foot skin reaction, bleeding, arterial thromboembolism and hematologic toxicities among patients received VEGF inhibitors [19–34]. Gastrointestinal (GI) perforation is a rare but serious adverse event associated with VEGF inhibitors. A previous meta-analysis demonstrated that the use of bevacizumab significantly increased the risk of GI perforation when compared with controls (RR2.14, 95%CI: 1.19–3.85, $p = 0.011$)[35]. While GI perforation associated with VEGFR-TKIs has been reported with a substantial variation in the incidences, ranging from 0 to 4.9% in clinical trials [36–38], there has been no systematic attempt to synthesize these data, thus the overall incidence and risk of GI perforation with VEGFR-TKIs has not been well defined. As GI perforation could be fatal in many instances due to severe peritonitis, it is important to fully recognize the risk of VEGFR-TKIs induced GI perforation. Therefore, we conducted this systematic review and meta-analysis to investigate the incidence and risk of GI perforation in patients treated with VEGFR-TKIs.

2. Methods

2.1. Data sources

We conducted an independent review of citations from PubMed between January 1, 1966, and March 31, 2013. Key words were sorafenib, nexavar, BAY43-9006, sunitinib, sutent, SU11248, pazopanib, votrient, GW786034, vandetanib, caprelsa, ZD6474, axitinib, cediranib, tivozanib, regorafenib, Cabozantinib, clinical trials and cancer. The search was limited to prospective clinical trials 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 March 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 Jan 2004 and Jan 2013. 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. We also reviewed the reference lists of the original and review articles to identify relevant studies.

2.2. Study selection

The primary goal of our study was to determine the overall incidence of GI perforation associated with VEGFR-TKIs and establish the association between treatments with VEGFR-TKIs and the risk of developing GI perforation. Thus, only prospective phase II and III trials evaluating VEGFR-TKIs in cancer patients with adequate data on GI perforation were incorporated in the analysis. Phase I trials were omitted due to multiple dose level and limited sample sizes. Clinical trials that met the following criteria were included: (1) prospective phase 2 or 3 trials involving cancer patients; (2) participants assigned to treatment with VEGFR-TKIs (alone or in combination at any dosage or frequency);

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