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Pancreatitis with vascular endothelial growth factor receptor tyrosine kinase inhibitors

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Contents

Abstract

A trial-level meta-analysis was conducted to determine the relative risk (RR) of pancreatitis associated with multi-targeted vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKI). Eligible studies included randomized phase 2 and 3 trials comparing arms with and without an FDA-approved VEGFR TKI (sunitinib, sorafenib, pazopanib, axitinib, vandetanib, cabozantinib, ponatinib,

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regorafenib). Statistical analyses calculated the RR and 95% confidence intervals (CI). A total of 10,578 patients from 16 phase III trials and 6 phase II trials were selected. The RR for all grade and high-grade pancreatitis for the TKI vs. no TKI- arms was 1.95 ($p = 0.042$, 95% CI: 1.02 to 3.70) and 1.89 ($p = 0.069$, 95% CI: 0.95 to 373), respectively. No differential impact of malignancy type or specific TKI agent was seen on RR of all grade of high grade pancreatitis. Better patient selection and monitoring may mitigate the risk of severe pancreatitis.

Keywords: Vascular endothelial growth factor receptor; Tyrosine kinase inhibitors; Approved; Pancreatitis; Meta-analysis

1. Introduction

Several multi-targeted vascular endothelial growth factor receptor (VEGFR) tyrosine-kinase inhibitors (TKI) agents have been approved by the U.S. FDA including sunitinib, sorafenib, pazopanib, axitinib, vandetanib, cabozantinib, ponatinib and regorafenib. These agents have improved clinical outcomes in a wide range of malignancies including renal cell carcinoma (RCC), hepatocellular cancer (HCC), gastro-intestinal stromal tumor (GIST), medullary thyroid cancer (MTC), colorectal cancer, chronic myeloid leukemia and pancreatic neuroendocrine tumors.

However, VEGFR TKIs are also associated with rare but severe life threatening toxicities, especially cardiovascular events and hemorrhage [1–3]. Several case reports have reported acute pancreatitis as an adverse event associated with sorafenib, and a phase II trial has suggested a high incidence with ponatinib [4–9]. However, the association of VEGFR TKIs with pancreatitis has not been addressed in a systematic manner. In order to determine the risk of pancreatitis associated with all of the currently approved VEGFR TKIs, we performed a meta-analysis of randomized clinical trials (RCT) published or presented in major oncology conferences.

2. Methods

2.1. Selection of studies

An independent review of citations in the English language from PubMed/Medline from January 1966 to December 2013 was conducted. We searched individual VEGFR TKIs: sunitinib, sorafenib, pazopanib, axitinib, vandetanib, cabozantinib, ponatinib and regorafenib and narrowed the search to RCTs. Abstracts and virtual meeting presentations from major conferences (ASCO, ESMO, AACR), the most recent reports, updated manufacturer's package inserts and clinicaltrials.gov were also searched. In clinicaltrials.gov, we used the advanced search option to search individual VEGFR TKI, and narrowed the search by entering 'randomized' in the interventions option. Phase 2 and 3 RCTs comparing arms with and without a VEGFR TKI were selected. We excluded trials that contained a VEGF inhibitor in all arms. Study quality was assessed by using the seven-point Jadad ranking system [10]. Trials that did not list pancreatitis as an adverse event in any arm were excluded.

2.2. Data extraction and clinical end points

Data abstraction was conducted independently by 3 investigators (PG, CM, GS) according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [11]. The variables extracted are shown in Table 1. High grade pancreatitis events require inpatient hospitalization for pain, vomiting or nutritional support (grade 3), or are life-threatening (grade 4) or result in persistent or significant disability, and may lead to death (grade 5). According to the Common Terminology Criteria for Adverse Events (CTCAE) v. 4.0, grade 2 pancreatitis consists of radiographic changes of pancreatitis or enzyme elevations without symptoms. However, for our meta-analysis, we excluded events recorded as solitary enzyme elevations, limiting our data to cases recorded as pancreatitis in order to avoid capturing duplicate entries (i.e. recording lipase/amylase elevation and pancreatitis as two separate events for the same patient) leading to over-estimation of pancreatitis. Additionally, enzyme elevations can be non-specific and may not represent clinically relevant pancreatitis.

2.3. Statistical analysis

Statistical analyses were performed by using R statistical software, version 3.0 [12,13]. Trials were considered evaluable for one or both categories of all grades or high-grade (grade ≥ 3) of pancreatitis based on reporting in the safety profiles of trials. Sub-analyses were performed for risk of pancreatitis based on malignancy type. The proportion of patients with pancreatitis and the 95% confidence intervals (CIs) were derived for each arm of each study and used to calculate the relative risk (RR) of pancreatitis. For studies reporting zero events in an arm, the classic half-integer correction was applied to calculate the RR and variance.

For the meta-analysis, both the fixed-effects model and the random-effects model were considered. The latter was calculated with the method of DerSimonian and Laird, which considers both within-study and between-study variation [14]. Statistical heterogeneity among studies included in the meta-analysis was assessed using the Cochrane's Q statistic, and inconsistency was quantified with the I^2 (I-squared) statistic, which is used to describe the percentage