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Hepatotoxicity with vascular endothelial growth factor receptor tyrosine kinase inhibitors: A meta-analysis of randomized clinical trials

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Contents

Abstract

A meta-analysis of randomized controlled trials (RCT) was conducted to determine the relative risk (RR) of hepatotoxicity with vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKI). Citations from PubMed/Medline, abstracts from major

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conferences, clinicaltrials.gov and package inserts were reviewed to include RCTs comparing arms with or without a VEGFR TKI. The RRs of all-grade ALT, AST, ALP and bilirubin elevation in 18,282 patients from 52 trials were 1.57 (95% CI 1.38–1.79, $p < 0.001$), 1.57 (95% CI 1.36–1.81, $p < 0.001$), 1.20 (95% CI 1.09–1.83, $p < 0.001$) and 1.55 (95% CI 1.21–1.97, $p < 0.001$) respectively, and high-grade elevations were 1.66 (95% CI 1.25–2.20, $p = 0.001$), 1.61 (95% CI 1.21–2.14, $p = 0.001$), 1.02 (95% CI 0.70–1.47, $p = 0.932$) and 1.34 (95% CI 1.0–1.81, $p = 0.054$) respectively compared to those in the non-TKI group. The incidence of hepatic failure with VEGFR TKIs was 0.8%.
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Keywords: Vascular endothelial growth factor receptor; Tyrosine kinase inhibitors; Approved; Hepatotoxicity; Meta-analysis

1. Introduction

Several multi-targeted vascular endothelial growth factor receptor (VEGFR) tyrosine-kinase inhibitors (TKI) have been approved by the U.S. Food and Drug Administration (FDA) in the past decade – sunitinib, sorafenib, pazopanib, axitinib, vandetanib, cabozantinib, ponatinib and regorafenib. Limited post-marketing experience, underreporting, difficulty in diagnosis and poor follow-up time of exposed patients, has made it difficult to estimate the adverse effects of these agents, especially hepatotoxicity, which can take several weeks to develop and often just manifest as liver enzyme elevation [1]. In an effort to balance the safety and efficacy of drugs, regulatory agencies have published several guidelines for premarketing evaluation of hepatotoxicity [2–5]. However, the overall risks of such events are largely underreported. Here we conduct a trial-level meta-analysis of hepatotoxicity associated with the use of VEGFR TKIs. Pooling multiple studies in a meta-analysis can help increase the sample size and thus the power to study such rare adverse events of interest.

Several VEGFR TKIs have been reported to cause hepatotoxicity. The potential for serious hepatotoxicity with sunitinib, regorafenib, ponatinib and pazopanib is believed to be sufficiently high requiring a boxed label warning by FDA. Mueller and colleagues [6] reported a case of fatal fulminant hepatitis after 5 months of treatment with sunitinib in a 75-year old woman with metastatic renal cancer. Similarly, several case reports report hepatotoxicity with sorafenib [7–11]. A meta-analysis was performed evaluating the hepatotoxicity of TKIs, however its size was limited to 12 trials and did not focus on VEGFR TKIs [12].

Vague symptoms such as fatigue, anorexia, nausea, discomfort in the right upper quadrant, and dark urine may be the first clues that hepatotoxicity has occurred [13]. Biochemical markers of liver injury include elevation of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and bilirubin. Another measurable liver function is protein synthesis, which is reflected in the albumin concentration and the prothrombin time (PT). Regulatory authorities and drug developers have relied on Hy's rule, named after the late Professor Hyman Zimmerman, which predicts post-approval risk of serious hepatotoxicity [14]. A case that meets Hy's rule criteria is defined as a patient with concurrent elevation in ALT greater than three times the ULN (upper limit of normal) and total bilirubin greater than twice the ULN with no evidence of biliary obstruction (e.g. elevation of alkaline phosphatase) or of other causes that can reasonably explain these elevations in ALT and bilirubin. When the above criteria for acute liver failure are considered to have been met, Hy's rule predicts a mortality rate that can exceed 10%.

2. Methods

2.1. Selection of studies

An independent review of citations in the English language from PubMed/Medline from January 1966 to March 2014 was conducted. Key words included in the search were RCT, sunitinib, sorafenib, pazopanib, axitinib, vandetanib, cabozantinib, ponatinib and regorafenib. Abstracts and virtual meeting presentations from major conferences – American society of clinical oncology (ASCO), European society of medical oncology (ESMO), and American association of cancer research (AACR) – were reviewed from January 2008 to April 2014. Updated manufacturer's package inserts and clinicaltrials.gov were also searched. Phase II and III RCTs comparing arms with and without a VEGFR TKI were selected. Since the objective of this analysis was to quantify the differences in incidence of hepatotoxicity in the TKI arm compared to placebo arm, phase I trials, single-arm studies and studies which did not report any liver adverse events were excluded. We excluded trials that contained a VEGF inhibitor or a TKI in all arms. Study quality was assessed by using the seven-point Jadad ranking system [15].

2.2. Data extraction and primary end points

Data abstraction was conducted independently by 4 investigators (PG, NM, YJ, GS) according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [16]. The variables extracted are shown in Table 1 . We define hepatotoxicity as injury to the liver which can lead to impairment of liver function and later symptoms related to liver failure. The primary endpoints of the study are all and high-grade elevation of ALT, AST, ALP or total bilirubin was recorded as marker for hepatic injury. Trials mentioning hepatic failure/dysfunction