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Congestive heart failure with vascular endothelial growth factor receptor tyrosine kinase inhibitors

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Contents

Abstract

A systematic review and meta-analysis was conducted to determine the relative risk (RR) of congestive heart failure (CHF) associated with approved multi-targeted vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKI). Eligible studies included randomized trials comparing arms with and without an FDA-approved VEGFR TKI. Statistical analyses calculated the relative risk (RR) and 95% confidence intervals (CI). A total of 10,647 patients from 16 phase III trials and 5 phase II trials were selected. All grade CHF occurred in 138 of 5752 (2.39%) patients receiving VEGFR TKIs and 37 of 4895 (0.75%) patients in the non-TKI group. High-grade CHF occurred in 17 of 1426 (1.19%) patients receiving VEGFR TKIs and 8 of 1232 (0.65%) patients in the non-TKI group. The RR of all grade and high-grade

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CHF for the TKI vs. no TKI arms was 2.69 ($p < 0.001$; 95% CI: 1.86 to 3.87) and 1.65 ($p = 0.227$, 95% CI: 0.73 to 3.70), respectively. The RR of relatively specific TKIs (axitinib) was similar to relatively non-specific TKIs (sunitinib, sorafenib, vandetanib, pazopanib).

Keywords: Vascular endothelial growth factor receptor; Tyrosine kinase inhibitors; Approved; Congestive heart failure; Meta-analysis

1. Introduction

Several multi-targeted vascular endothelial growth factor receptor (VEGFR) tyrosine-kinase inhibitors (TKI) agents have been approved by the United States FDA including sunitinib, sorafenib, pazopanib, axitinib, vandetanib, cabozantinib, ponatinib and regorafenib. As of March 2013, at least one of these TKIs was approved for renal cell carcinoma (RCC), hepatocellular cancer (HCC), gastro-intestinal stromal tumor (GIST), medullary thyroid cancer (MTC), chronic myeloid leukemia and pancreatic neuroendocrine tumors (PNET).

Meta-analyses have reported findings of congestive heart failure (CHF) with sunitinib and bevacizumab [1,2]. The incidence of all-grade CHF in sunitinib-treated patients was 4.1% in one meta-analysis [1]. Another meta-analysis evaluating fatal adverse events in patients treated with VEGFR TKIs reported 15% deaths from myocardial infarction and 2 cases with fatal CHF [3]. However, the risk of CHF has not been systematically studied across all approved VEGFR TKIs. Among the approved VEGFR TKIs, axitinib is known to be relatively specific for VEGFR 1, 2 and 3, while the other TKIs are relatively promiscuous and inhibit other targets such as RAF in the case of sorafenib, FLT3 in the case of sunitinib and EGFR in the case of vandetanib. No studies evaluate the risk of CHF in relatively specific TKIs (axitinib) compared to less specific TKIs (pazopanib, sunitinib, sorafenib, vandetanib, ponatinib, cabozantinib, regorafenib). Differential risks of CHF associated with the specificity of VEGFR TKIs may provide useful insights regarding the mechanism of cardiac dysfunction and future management. Hence, we performed a meta-analysis of randomized clinical trials (RCT) to determine the risk of CHF associated with all of the currently approved VEGFR TKIs for advanced malignancies, either 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 May 2013 was conducted. Key words included in the search were randomized clinical trial, sunitinib, sorafenib, pazopanib, axitinib, vandetanib, cabozantinib, ponatinib and regorafenib. 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.

The following adverse outcomes were considered as CHF: left ventricular dysfunction, left ventricular systolic dysfunction, cardiac failure, ventricular hypokinesia, congestive cardiac failure and decreased ejection fraction. Randomized phase II and III trials 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 [4]. Trials were considered for all grade and high grade (grade ≥ 3) CHF based on Common Terminology Criteria for Adverse Events (CTCAE) v. 4.0. Grade 2 events include CHF not requiring intervention; Grade 3 CHF events require intervention and Grade 4 CHF events usually include life-threatening dysfunction. Trials that either did not list CHF as an adverse event or reported no CHF in all arms were excluded.

2.2. Data extraction and clinical end points

Data abstraction was conducted independently by 2 investigators (PG and GS) according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [5]. The variables extracted are shown in Table 1.

2.3. Statistical analysis

Statistical analyses were performed by using R statistical software, version 3.0 [6,7]. The number of CHF events and patients receiving VEGFR TKIs were extracted from the safety profile for the trials. Trials were considered evaluable for one or both categories of grades of CHF based on reporting. The proportion of patients with those adverse outcomes and 95% confidence intervals (CIs) were derived for each arm of each study and used to calculate RR of CHF. 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 [8]. 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 of total variation across studies that is due to heterogeneity rather than chance; a value of 0% indicates no observed heterogeneity, while larger values between 0% and 100% show increasing