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Hand-foot skin reaction with vascular endothelial growth factor receptor tyrosine kinase inhibitors in cancer patients: A systematic review and meta-analysis

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ABSTRACT

A meta-analysis was conducted to systematically review the risk of hand-foot skin reaction (HFSR) with vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKIs) in patients with cancer. The relevant studies of the randomized controlled trials (RCTs) in cancer patients treated with VEGFR-TKIs were retrieved and the systematic evaluation was conducted. EMBASE, MEDLINE, and PubMed were searched for articles published till May 2017. Twenty-one RCTs and 9552 patients were included. The current analysis suggested that the use of VEGFR-TKIs increased the risk of all-grade HFSR (7.04;95%CI, 5.33–9.30;$p < 0.00001$) and high-grade (≥grade 3) HFSR (21.62;95%CI, 15.19–30.78;$p < 0.00001$). On subgroup analyses, the risk ratio (RR) of all-grade HFSR varies significantly according to cancer type, whereas the RR of high-grade HFSR did not. The risk of all-grade and high-grade HFSR did not affect by drug types, treatment line, median age and treatment duration.

1. Introduction

Angiogenesis is essential for tumor growth and blood borne metastasis, and this process is mainly driven by vascular endothelial growth factor (VEGF) (Quesada et al., 2007; Kamba and McDonald, 2007).

Anti-angiogenic therapy targeting VEGF signaling pathway can inhibit vascular growth and affect the survival of certain tumor cells. During the past decades, several VEGF receptor (VEGFR) tyrosine kinase inhibitors (TKIs) have been approved by the U.S. Food and Drug Adminis-tration (FDA), including regorafenib, vandetanib, cabozantinib, lenvatinib, axitinib, sunitinib, sorafenib, pazopanib, and cediranib. The use of VEGFR-TKIs had led to considerable improvements in the clinical outcome of patients with various tumor types (Polimeni and Gazzano, 2014; Folkman, 2002; Sharp et al., 2016).

Although targeted therapy lacks the typical adverse events of cytotoxic chemotherapy, several specific drug-related toxicities have been reported in patients.

The associated adverse events include fatigue, decreased appetite, nausea, diarrhoea, dehydration, hypertension, and dermatological manifestations (Elisei et al., 2013; Smith et al., 2013). Importantly, hand-foot skin reaction (HFSR), sometimes referred to as hand foot syndrome (HFS) or palmar-plantar erythrodysesthesia (PPE) is considered the most clinically significant dermatological adverse event for patients on some VEGFR-TKIs and can lead to detriment in quality of life (QoL) (Nardone et al., 2012; Sibaud et al., 2011) or interruptions in antineoplastic treatment (Lacouture et al., 2008a). Painful, tender, localized, erythematous lesions erupt and classically affect the palms and soles and any areas subject to increased friction (Balagula et al., 2010). For patients, these debilitating symptoms hinder their ability to perform activities of daily living and cause a significant financial burden, thus leading to a reduced quality of life (Lacouture et al., 2008b).

The HFSR with axitinib, regorafenib and sorafenib have been compared in previous systematic reviews (Fischer et al., 2013; Belum et al., 2013; Chu et al., 2008), respectively. However, the HFSR of VEGFR-TKIs was still poorly understood. Therefore, we conducted a systematic review of literature to identify therapeutic trials of VEGFR-TKIs and performed a meta-analysis of the published results to fully investigate the incidence and risk of HFSR.

2. Patients and methods

2.1. Search strategy and study selection

Study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher

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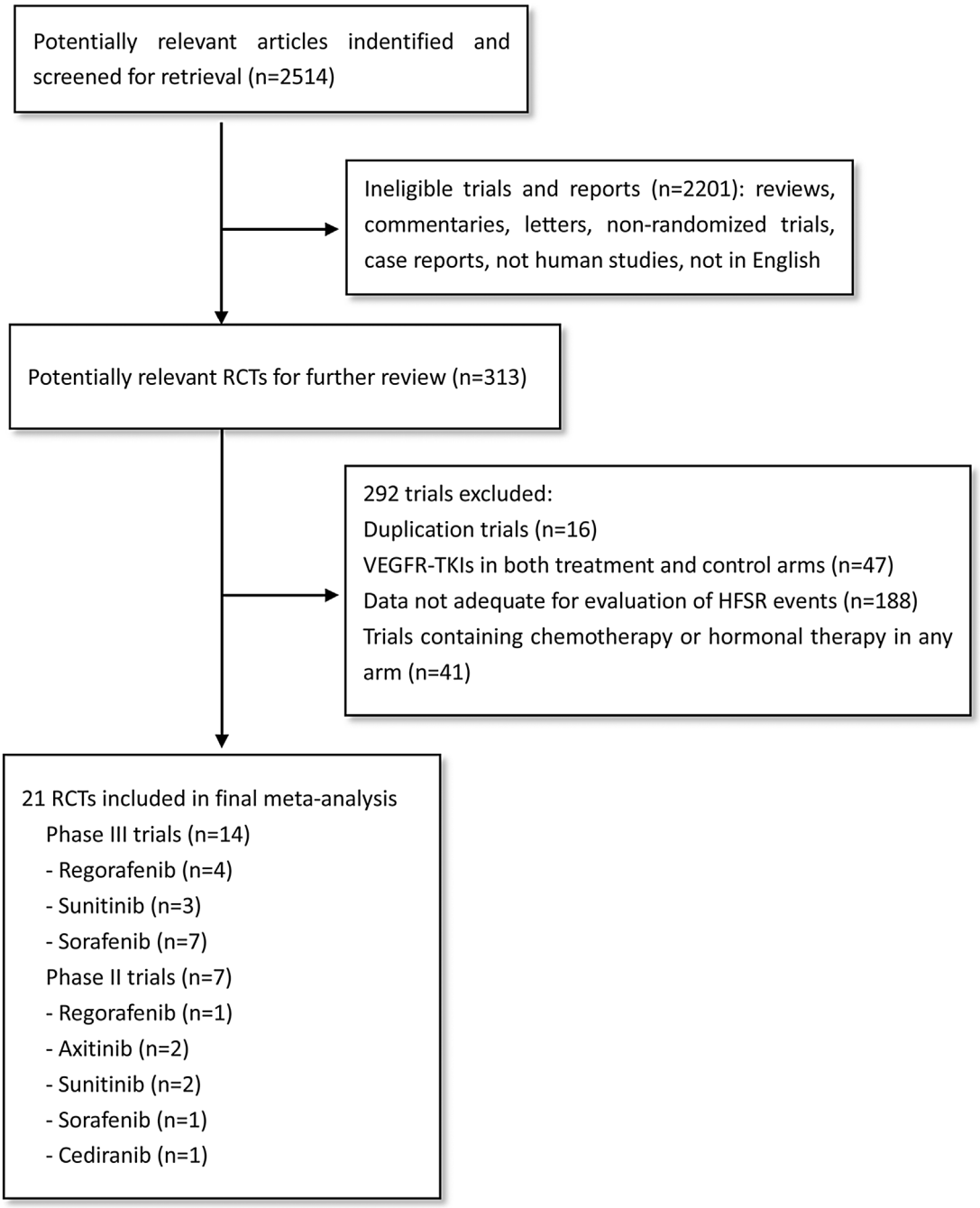

Fig. 1. Flow chart showing the selection of studies included in the present review.

et al., 2009) (supplement material). An independent review of citations from PubMed/Medline from January 1, 1966 to May 31, 2017 was conducted. Databases were searched using combinations of the following keywords 'regorafenib'; 'vandetanib'; 'cabozantinib'; 'lenvatinib'; 'axitinib'; 'sunitinib'; 'sorafenib'; 'pazopanib'; 'cediranib'; 'tumor'and 'cancer'. The search was limited to RCTs published in English. We also performed independent searches using EMBASE between January 1; 1974; and May 31; 2017; to ensure that no clinical trials were overlooked. Additionally; we searched the Cochrane Central Register of Controlled Trials to obtain information on the registered trials between January 2004 and May; 2017.

At each screening level, investigators of the review team selected articles for inclusion independently after an initial calibration exercise.

RCTs met the following criteria were included:

(1) Randomized controlled phase II and III trials in patients with cancer.
(2) Participants assigned to treatment with one of these agents daily.
(3) Events or event rate and sample size available for HFSR.
(4) Only trials containing pure placebo, best supportive care, observation or no therapy in the control arm were included.

As chemotherapeutic agents, hormonal agents or corticosteroids can modulate HFSR, we excluded trials where these agents were used concurrently.

2.2. Data extraction

We extracted details on study characteristics, treatment information, results, and safety profiles from selected trials. Data were