

Risk of hematologic toxicities in patients with solid tumors treated with everolimus: A systematic review and meta-analysis

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Accepted 7 June 2013

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Abstract

We performed a systematic review and meta-analysis of hematologic toxicities associated with everolimus, an oral mammalian target of rapamycin (mTOR) inhibitor. Eligible studies included phase II and III trials of patients with solid tumors on 10 mg of everolimus daily describing events of neutropenia, thrombocytopenia, anemia or lymphopenia. The incidence of everolimus-associated all-grade and high-grade

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(Grade 3–4) hematologic toxicities were, respectively: neutropenia: 21.7% and 3.6%; thrombocytopenia: 36.0% and 4.7%; anemia: 61.2% and 8.4% and lymphopenia: 40.9% and 14.9%. Everolimus was associated with an increased risk of all-grade neutropenia (RR = 2.24, [95% CI 1.51–3.32]), all-grade (RR = 9.19, [95% CI 4.51–18.70]) and high-grade (RR = 7.46, [95% CI 2.58–21.61]) thrombocytopenia, all-grade (RR = 1.58, [95% CI 1.25–1.99]) and high-grade (RR = 3.92, [95% CI 1.46–10.52]) anemia and all-grade (RR = 1.72, [95% CI 1.50–1.97]) and high-grade (RR = 2.70, [95% CI 1.86–3.93]) lymphopenia.

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Keywords: Everolimus; Meta-analysis; Hematologic toxicities; Anemia; Lymphopenia; Neutropenia; Thrombocytopenia

1. Introduction

Everolimus is an orally active rapamycin analog that inhibits the function of mammalian target of rapamycin (mTOR). The PI3K/AKT/mTOR pathway is frequently activated and plays a vital role in many human cancers [1]. The mTOR contains a serine–threonine protein kinase domain that mediates diverse and important cellular processes such as proliferation, differentiation, survival, motility, autophagy, and metabolism. Everolimus exerts its antitumor activity by forming a complex with the FK binding protein complex (FKBP-12), which specifically binds the mTOR [2].

Currently, the United States Food and Drug Administration (FDA) has approved everolimus for patients with advanced renal cell carcinoma (RCC) resistant to sunitinib or sorafenib [3], subependymal giant cell astrocytoma associated with tuberous sclerosis [4], progressive neuroendocrine tumors of pancreatic origin (PNET) [5], advanced hormone receptor-positive, HER2-negative breast cancer [6] and subependymal giant cell astrocytoma (SEGA) [7].

mTOR inhibitors, including everolimus and temsirolimus, have been accompanied by a unique spectrum of adverse events, which are different from traditional cytotoxic anticancer therapies. For instance, previous meta-analyses have shown an increased risk of all- and high-grade pneumonitis (incidence: 10.4% and 2.4%, respectively) [8], all-grade rash (28.6%) [9], all-grade stomatitis (44.3%) [10], and high-grade metabolic complications (11.0%) including hyperglycemia, hypercholesterolemia, and hypertriglyceridemia [11]. Additionally, hematologic toxicities associated with everolimus have been reported in randomized controlled trials. However, there has been a substantial variation in the incidence among clinical trials. There has been no systematic attempt to synthesize these data and the overall risk of hematologic toxicities induced by everolimus has yet to be defined. Therefore, we conducted a systematic review and meta-analysis of available clinical trials to determine the overall incidence and risk of developing hematologic toxicities in patients treated with everolimus.

2. Methods

2.1. Data source

We conducted an independent review of Medline databases from January 1966 to January 2013 using

“everolimus” as a search keyword. The search was limited to human, cancer, and clinical trials published in English. We manually searched abstracts and presentations containing the same search term “everolimus” from the American Society of Clinical Oncology (ASCO) conferences held between January 2006 and January 2013 to search for relevant trials. An independent search of the Web of Science, Embase and Cochrane electronic databases was also performed to ensure that no additional clinical trials had been overlooked. In cases of duplicate publications, only the most complete, recent, and updated report of the clinical trial was included. Finally, the most updated package insert from everolimus was reviewed to identify relevant information [12]. Trials were selected and systemically reviewed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [13].

2.2. Study selection

Clinical trials that met the following criteria were included (1) phase II and III trials in patients with solid tumors; (2) participants assigned to treatment with everolimus at a dose of 10 mg orally once daily; and (3) events or event rate and sample size available for all-grade or high-grade ($\geq$ grade 3) hematologic toxicities including neutropenia, thrombocytopenia, anemia and lymphopenia. For incidence analysis, trials that assigned participants to everolimus monotherapy were used to define the incidence of hematologic toxicities associated with everolimus as a single agent. For relative risk analysis, we included trials that randomly assigned participants to either everolimus versus placebo or control drug in addition to the same treatment to avoid potential confounders in the risk of hematologic toxicities. Phase I trials were excluded because of the different drug dosages as well as the small number of patients in these trials. Independent reviewers (T.F and A.L.) screened reports that included the key term by their titles and abstracts for relevance. Then, full texts of the relevant articles were retrieved to assess eligibility. The references of relevant reports were also reviewed manually.

2.3. Data extraction and clinical end points

Two investigators (T.F and A.L.) independently performed data extraction. The following information was recorded for each study: first author's name, year of publication, trial

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