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Complications of Treatment

Metabolic complications with the use of mTOR inhibitors for cancer therapy

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ABSTRACT

Background: mTOR inhibitors are now approved by regulatory agencies for the treatment of a variety of malignancies. The risk of metabolic complications with these agents is not well characterized.
Methods: PubMed was searched for articles published from 2001 until 2011. Eligible studies included prospective randomized trials evaluating temsirolimus, everolimus, and ridaforolimus in patients with all solid tumor malignancies. Sixteen eligible phase II clinical trials and 8 randomized controlled clinical trials were included in a systematic review and meta-analysis and the number of metabolic related AEs (hyperglycemia, hypercholesterolemia, and hypertriglyceridemia) was extracted. Incidence rates and incident rate ratios were calculated.
Findings: Twenty-four trials, including 4261 patients, were included in the calculation of the incidence rate. The average incidence rate of all grade metabolic related events was 0.70 (95% CI, 0.47, 0.93). The average incidence rate of serious (grade 3 and 4) metabolic related adverse events was 0.11 (95% CI, 0.08, 0.15). The incidence rate ratio (IRR) of a metabolic adverse event with mTOR inhibitor therapy compared with control was 2.93 (95% CI, 2.33, 3.70) and of serious grade 3 and 4 metabolic adverse events was 4.58 (95% CI, 2.86, 7.34). The IRR of all grade hyperglycemia was 2.95 (95% CI, 2.14, 4.05) and of grade 3–4 hyperglycemia was 5.25 (95% CI, 3.07, 9.00). The IRR of all grade hypertriglyceridemia was 2.49 (95% CI, 1.76, 3.52) and of grade 3–4 hypertriglyceridemia was 2.01 (95% CI, 0.65, 6.27). The IRR of all grade hypercholesterolemia was 3.35 (95% CI, 2.17, 5.18) and of grade 3–4 hypercholesterolemia was 6.51 (95% CI, 1.48, 28.59). These findings suggest a statistically significant increase in the risk of hyperglycemia, hypercholesterolemia (all grades and grade 3 and 4), and all grade hypertriglyceridemia associated with mTOR therapy when compared with control.
Interpretation: The risk of all grade and grade 3–4, hyperglycemia, hypercholesterolemia, and hypertriglyceridemia, are increase in patients treated with mTOR inhibitors compared with control.

Introduction

As our understanding of tumor biology has become more sophisticated, cancer therapeutics have shifted from traditional cytotoxic chemotherapy towards molecularly targeted agents. This shift has not only been accompanied by differences in mode of administration (e.g., frequently oral) and mechanisms of anticancer activity (e.g., frequently cytostatic) but also by a marked change in adverse event profiles. Though side effects of anticancer therapy were once dominated by transient myelosuppresion and nausea/vomiting, this new generation of therapies has generally been characterized by more chronic toxicities affecting a diverse range of organ systems. The team of specialists required to support patients being maintained on such therapies has expanded beyond oncologists, to include dermatologists, endocrinologists, pulmonologists, cardiologists, and others. An understanding of the likelihood, and severity, of particular side effects accompanying each new class of agent is therefore critical to optimizing patient management.

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The mammalian target of rapamycin (mTOR) pathway is vital to cell processes such as proliferation, cell growth, metabolism, and angiogenesis.[1,2] This critical role prompted the development and exploration of several pharmacologic inhibitors of the mTOR pathway for cancer therapy.[3–23] Currently, two mTOR inhibitors have been approved for the treatment of cancer by the United States Food and Drug Administration (FDA). Temsirolimus has been approved for treatment of advanced renal cell carcinoma (RCC) while everolimus has been approved for RCC, pancreatic neuroendocrine tumors (PNET), and for subependymal giant cell astrocytoma associated with tuberous sclerosis. Ridaforolimus, although not yet FDA approved, is currently in phase III clinical trials.

The incidence of most cancers increases with age and risk factors for certain cancers (e.g., smoking) are also associated with an increased risk of other chronic illnesses. As a result, many patients with cancer have comorbidities including diabetes and cardiovascular disease. Metabolic toxicities have emerged as a common, and unique, side effect of mTOR inhibitors. Given the potential for these side effects to influence the comorbidities and general health of patients treated with mTOR inhibitors, we conducted a systematic review and meta-analysis of all published RCTs to characterize the incidence and risk of metabolic complications with mTOR inhibitors.

Methods

Data source

Study selection was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[24] An independent review of citations from PubMed published from January 1, 1997 until May 30, 2011 was conducted. Keywords included in the search were: *temsirolimus*, *everolimus*, and *ridaforolimus*. The search was limited to articles published in the English language. Abstracts and presentations containing the terms *temsirolimus*, *everolimus*, and *ridaforolimus* from the American Society of Clinical Oncology (www.ASCO.org) held between January 1997 and May 30, 2011 also were searched to identify relevant clinical trials; however, only trials published in peer-reviewed publications, in full manuscript form, or phase III trials with adequate adverse event reporting were included. Each publication was reviewed and in cases of duplicate publication only the most complete, recent, and updated report of the clinical trial was included in the meta-analysis.

Study selection

The primary objectives of this study were to evaluate the incidence of metabolic side effects (hyperglycemia, hypercholesterolemia, and hypertriglyceridemia) with mTOR inhibitors and the association between treatment with mTOR inhibitors and the development of such side effects. For incidence calculations, clinical trials that met the following criteria were included: (1) phase II and III trials of patients with solid tumors, (2) treatment with an mTOR inhibitor, (3) available data on metabolic side effects. For incidence rate ratio calculations, the selection criteria were the same but only trials that included a random assignment of participants to treatment with an mTOR inhibitor versus control (standard of care, placebo, or best supportive care) were included. Trials with combination therapy, which included an mTOR inhibitor as a component of the treatment regimen, were also included unless combined with a cytotoxic agent. For trials in which there were multiple arms, we pooled the adverse events for the arms that contained the mTOR inhibitor as long as the dosing schedule was the same.

Data extraction and clinical end point

We extracted data on study characteristics, treatment information, and follow-up. The primary end points of the analysis were all grade and severe hyperglycemia, all grade and severe hypercholesterolemia,

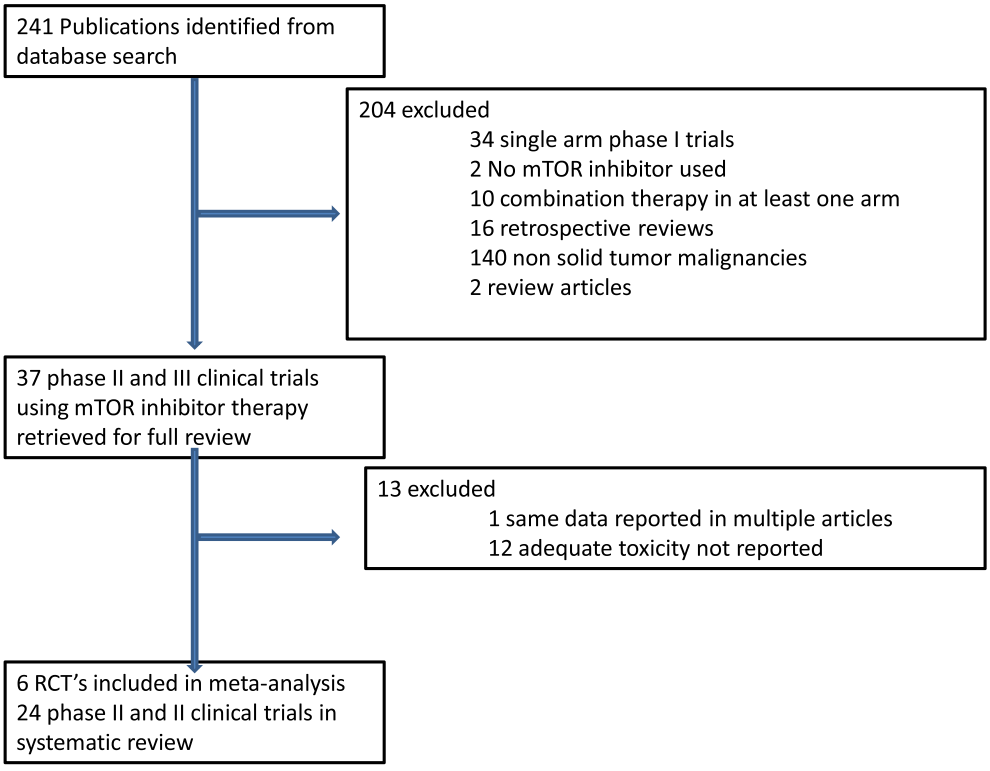

Fig. 1. Selection of phase 2 and 3 clinical trials included in the systematic review and selection of randomized controlled clinical trials (RCT's) for meta-analysis.