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Original Research

Statins and survival outcomes in patients with metastatic renal cell carcinoma

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Abstract ***Background:*** A growing body of evidence has demonstrated the anti-neoplastic activity of statins. The objective of this study was to investigate the effect of statin use on survival in patients with metastatic renal cell carcinoma (mRCC) treated in the modern therapy era.

Patients and methods: We conducted a pooled analysis of mRCC patients treated on phase II and III clinical trials. Statistical analyses were performed using Cox regression and the Kaplan–Meier method.

Results: We identified 4736 patients treated with sunitinib ($n = 1059$), sorafenib ($n = 772$), axitinib ($n = 896$), temsirolimus ($n = 457$), temsirolimus + interferon (IFN)-α ($n = 208$), bevacizumab + temsirolimus ($n = 393$), bevacizumab + IFN-α ($n = 391$) or IFN-α ($n = 560$), of whom 511 were statin users. Overall, statin users demonstrated an improved overall survival (OS) compared to non-users (25.6 versus 18.9 months, adjusted hazard ratio [aHR] 0.801, 95% confidence interval [CI] 0.659–0.972, $p = 0.025$). When stratified by therapy type, a benefit in OS was demonstrated in statin users compared to non-users in individuals receiving therapy targeting vascular endothelial growth factor (28.4 versus 22.2 months, aHR 0.749, 95% CI 0.584–0.961, $p = 0.023$) or mammalian target of rapamycin (18.6 versus 14.0 months, aHR

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0.657, 95% CI 0.445–0.972, $p = 0.035$) but not in those receiving IFN-α (15.6 versus 14.8 months, aHR 1.292, 95% CI 0.703–2.275, $p = 0.410$). Adverse events were similar between users and non-users.

Conclusions: We demonstrate that statin use may be associated with improved survival in patients with mRCC treated in the targeted therapy era. Statins could represent an adjunct therapy for patients with mRCC; however, this is hypothesis generating and requires prospective evaluation.

1. Introduction

Statins are a class of drugs that reduce cholesterol by inhibiting HMG-CoA reductase, the rate-limiting enzyme involved in cholesterol biosynthesis [1]. They are the cornerstone of therapy for patients with hypercholesterolaemia and are used to prevent and treat cardiovascular disease. Statins are among the most commonly prescribed drugs worldwide and their use has been increasing over the past decade.

A growing body of preclinical studies has demonstrated the anti-neoplastic activity of statins. At the cellular level, statins have been linked to blocking cell-cycle progression, inducing apoptosis, and inhibiting cell-signaling pathways involved in tumour invasion and metastasis [1]. *In vivo* studies in animal models have further demonstrated the anti-proliferative effects of statins [2]. In humans, recent observational studies have shown that statin use is associated with a decreased risk of cancer-specific mortality in prostate, colorectal and breast cancer [3–5]. Several clinical trials have investigated the efficacy of statins on survival in patients with cancer; however, these were limited in size and results are inconclusive [6].

Studies exploring the benefits of statins in renal cell carcinoma (RCC) are widely lacking. Previous epidemiological studies of statins and the risk of RCC provide conflicting results with some studies demonstrating a reduced overall risk [7, 8], some showing no association [9–13], and a single study demonstrating an increased risk [14]. Several studies explore the association between statin use and disease progression in localized RCC. In one analysis, statin use was associated with a 33% recurrence risk reduction following surgery. No observational study to date has evaluated the effect of statins on survival in metastatic RCC (mRCC). One clinical trial in RCC patients with bone metastases explored the combination of zoledronic acid with fluvastatin or atorvastatin on bone biomarkers and skeletal events [15]. This pilot study of 11 patients, 6 of whom received concurrent targeted therapy, demonstrated that combination therapy affected certain bone biomarkers but did not consistently improve skeletal events. The trial did not document survival. The efficacy of statins combined with modern therapies targeting the vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) pathways has not been broadly described.

Currently, no study to date has evaluated the effect of statins in patients with mRCC treated with targeted therapy. Elucidation of the impact of statins in this population is highly relevant to optimizing the evolving treatment landscape for patients with metastatic disease. In this analysis, we utilize a large clinical trials database to investigate the effect of statins on survival outcomes in patients with mRCC treated in the targeted therapy era.

2. Patients and methods

2.1. Study design

We conducted a pooled analysis of patients with mRCC treated on phase II (NCT00054886, NCT00077974, NCT00267748, NCT00338884, NCT00137423 and NCT00835978) and phase III (NCT00083889, NCT00065468, NCT00678392, NCT00474786, NCT00631371 and NCT00920816) clinical trials sponsored by Pfizer. We identified 4736 patients treated for mRCC between January 2003 and June 2013. Patients who did not receive at least one dose of study treatment or had missing concomitant medication information were excluded from the multivariate analysis ($n = 720$).

Baseline demographic, clinical and laboratory data were collected. Statin users were defined as patients receiving a statin at baseline. The decision to start a statin and choice of agent was at the discretion of the treating physician. Patient follow-up consisted of imaging assessment every 4–12 weeks until disease progression or withdrawal. Treatment-associated toxicities were defined and evaluated according to the Common Terminology Criteria for Adverse Events, version 3.0.

2.2. Treatment outcomes

Overall survival (OS) was defined as the time from initiation of therapy to death from any cause. Progression-free survival (PFS) was defined as the time from initiation of therapy to date of progression or death from any cause, whichever came first.