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Original article

The association of statin therapy with clinicopathologic outcomes and survival among patients with localized renal cell carcinoma undergoing nephrectomy

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Abstract

Objectives: Although statins have been found to induce apoptosis and demonstrate antimetastases activity both in vitro and in vivo for renal cell carcinoma (RCC), clinical evidence of a role for these medications is limited. We evaluated the association of statin therapy with outcomes among patients with surgically treated localized RCC.

Methods and materials: We reviewed 2,357 patients who underwent nephrectomy between 1995 and 2009 for pNx/0, M0 RCC. Of these, 630 (27%) were taking statins within 3 months of surgery. Progression-free survival, cancer-specific survival, and overall survival were estimated using the Kaplan-Meier method. The associations of statin use with clinicopathologic outcomes were evaluated with multivariable logistic and proportional hazards regression models.

Results: Statin therapy at the time of nephrectomy was not significantly associated with the risks of locally advanced (pT3–4) pathologic tumor stage (odds ratio = 0.96; $P = 0.80$) or high (3–4) tumor grade (odds ratio = 1.11; $P = 0.30$). Median postoperative follow-up was 7.8 years. Compared with patients not on statin therapy, patients taking statins at surgery had similar 10-year progression-free survival (80% vs. 79%; $P = 0.56$), cancer-specific survival (85% vs. 84%; $P = 0.71$), and overall survival (59% vs. 64%; $P = 0.11$). On multivariable analysis, statin use was not significantly associated with the risks of disease progression (hazard ratio [HR] = 1.22; $P = 0.10$), death from RCC (HR = 1.02; $P = 0.90$), or all-cause mortality (HR = 0.84; $P = 0.05$).

Conclusions: We found no independent association between preoperative statin therapy and oncologic outcomes among patients with surgically treated localized RCC. Our data thus do not support an anticancer role for statin therapy in this setting.

Keywords: Statin; HGM-CoA reductase inhibitor; Renal cell carcinoma; localized; Nephrectomy

1. Introduction

Statins, which inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, have been used extensively for the treatment of hypercholesterolemia and prevention of cardiovascular events since their approval in 1987 [1]. Evidence suggests that statins contain antineoplastic properties as well, through the inhibition of cellular proliferation, induction of apoptosis, and reduction in angiogenesis [2,3]. Specifically, HMG-CoA reductase inhibitors halt the conversion of HMG-CoA to mevalonate, a critical component in the maintenance of cellular membrane integrity, signaling, protein synthesis, and cell cycle progression [2,4]. As mutant p53 transcriptionally activated mevalonate pathway genes play a vital role in tumorigenesis [5], a disruption of

Take home message: Despite the mechanistic data supporting antitumor activity of HMG-CoA reductase inhibitors in renal cell carcinoma (RCC), we found no independent association between statin use and cancer progression, RCC-specific, or all-cause mortality among patients with localized RCC undergoing nephrectomy.

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these uncontrolled cellular processes may thereby inhibit cancer growth and progression [6]. Indeed, anticancer properties of statins have been demonstrated among multiple solid malignancies, including prostate [7–10], colorectal [11,12], and breast cancers [13,14].

For renal cell carcinoma (RCC), in vitro and in vivo evidence suggests antitumor effects of statins through the modulation of multiple cellular processes, including the mTOR and JAK2/STAT3 pathways [15–17]. However, despite such mechanistic data supporting activity of HMG-CoA reductase inhibitors in RCC, the clinical utility of such therapy remains unclear. Epidemiological studies assessing primary prevention have demonstrated variable results [18–20]. Meanwhile, there remains paucity of data regarding the potential therapeutic implications for statin use among patients undergoing treatment for RCC [21–23]. Herein, then, we evaluated the association of statin use with clinicopathologic outcomes and survival among patients with localized RCC undergoing nephrectomy.

2. Materials and methods

Following Institutional Review Board approval, we reviewed the Mayo Clinic Renal Tumor Registry to identify 2,357 patients treated with radical or partial nephrectomy for sporadic, unilateral, and localized (pNx/0, M0) RCC at our institution between 1995 and 2009.

Clinical variables recorded included age, sex, year of surgery, type of surgery, symptoms at presentation, smoking status, Eastern Cooperative Oncology Group (ECOG) performance status, Charlson comorbidity index, and body mass index (BMI). The medical record was reviewed to identify patients with documented statin use within 3 months before surgery. Patients with a palpable flank or abdominal mass, discomfort, gross hematuria, acute-onset varicocele, or constitutional symptoms including rash, sweats, weight loss, fatigue, early satiety, and anorexia were considered symptomatic.

Pathologic features studied included histologic subtype, tumor size, 2010 primary tumor classification, nuclear grade, coagulative tumor necrosis, and sarcomatoid differentiation. A genitourinary pathologist (J.C.C.) reviewed the microscopic slides from all specimens without the knowledge of patient outcome. Follow-up after nephrectomy was generally quarterly for the first 2 years, semiannually for the next 2 years, and annually thereafter for patients without evidence of recurrent disease. For survival end points, vital status was identified from death certificates or physician correspondence. For patients followed elsewhere, the nephrectomy registry monitors outcomes annually by correspondence with the patient and the local treating physician.

Comparisons of clinicopathologic features between patients with and without statin use were performed using Wilcoxon rank sum and chi-square tests, as appropriate. Associations with advanced stage (pT3 or pT4) and high-grade (3 or 4) tumors at nephrectomy were evaluated using logistic regression models. Progression-free survival, cancer-specific survival (CSS), and overall survival (OS) were estimated as the time from nephrectomy to event or last follow-up using the Kaplan-Meier method. Disease progression was defined as distant metastases or death due to RCC. Cox proportional hazards regression models were used to evaluate the association of statin use with outcomes.

Moreover, associations with time to disease progression and death due to RCC after accounting for the competing risk of death without disease progression or death due to non–RCC-related causes were evaluated using a proportional subdistribution model [24]. In all logistic and proportional hazards regression models, year of surgery was used as a stratification effect to account for changes in clinicopathologic features and patient outcome over time. Finally, to evaluate the findings of Hamilton et al. [21] in our own data set, an identical multivariable model to the one from that study was tested, including age at surgery, sex, race (African American vs. other), type of surgery, Charlson comorbidity index, primary tumor classification, preoperative estimated glomerular filtration rate (calculated using the CKD-EPI equation), symptoms, and year of surgery (analyzed as a stratification effect).

$P < 0.05$ was considered statistically significant. Statistical analyses were performed using the SAS software package (SAS Institute, Cary, NC).

3. Results

Of the 2,357 patients who underwent radical or partial nephrectomy at our institution between 1995 and 2009, 630 (27%) had documentation of statin use within 3 months of surgery (Table 1). Clinicopathologic features for patients with and without statin use are provided in Table 2. As can be seen, patients treated with statin therapy were older (median age 66 vs. 61; $P < 0.001$), more likely to be male (71% vs. 65%; $P = 0.01$), have a greater Charlson index (median = 1 vs. 0; $P < 0.001$), worse ECOG performance score (≥ 1, 15% vs. 12%; $P = 0.05$), local or constitutional symptoms, greater BMI (median = 30 vs. 28; $P < 0.001$), incidence of obesity (BMI $\geq$ 30, 49% vs. 39%;

Table 1
Statin medication use at time of nephrectomy

Medication	n (%)[a]
Atorvastatin	329 (52)
Simvastatin	259 (41)
Lovastatin	38 (6)
Pravastatin	37 (6)
Rosuvastatin	24 (4)
Fluvastatin	17 (3)
Cerivastatin	2 (<1)

[a] $n = 558$ On 1 statin within 3 months of surgery, $n = 68$ on 2 statins, and $n = 4$ on 3 statins.