The Association between Statin Medication and Progression after Surgery for Localized Renal Cell Carcinoma

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Abbreviations and Acronyms

BMI = body mass index

GFR = glomerular filtration rate

RCC = renal cell carcinoma

Accepted for publication October 23, 2013.

Study received institutional review board approval.

Supported by the Steven Hanson Family Kidney Cancer Research Fund.

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Purpose: Evidence suggests that statins may influence pathways of renal cell carcinoma proliferation, although to our knowledge no study has examined the influence of statin medications on the progression of renal cell carcinoma in humans.

Materials and Methods: We identified 2,608 patients with localized renal cell carcinoma who were treated surgically between 1995 and 2010 at our tertiary referral center. Competing risks Cox proportional hazards models were used to evaluate the relationship between statin use and time to local recurrence or progression (metastases or death from renal cell carcinoma) and overall survival. Statin use was modeled as a time dependent covariate as a sensitivity analysis. Models were adjusted for clinical and demographic features.

Results: Of 2,608 patients 699 (27%) were statin users at surgery. Statin users had similar pathological characteristics compared to nonusers. At a median followup of 36 months there were 247 progression events. Statin use was associated with a 33% reduction in the risk of progression after surgery (HR 0.67, 95% CI 0.47–0.96, $p = 0.028$) and an 11% reduction in overall mortality that was not significant (HR 0.89, 95% CI 0.71–1.13, $p = 0.3$). Modeling statin use as a time dependent covariate attenuated the risk reduction in progression to 23% (HR 0.77, $p = 0.12$) and augmented the risk reduction in overall survival (HR 0.71, $p = 0.002$).

Conclusions: In our cohort statin use was associated with a reduced risk of progression and overall mortality, although this effect was sensitive to the method of analysis. If validated in other cohorts, this finding warrants consideration of prospective research on statins in the adjuvant setting.

Key Words: kidney neoplasms, hydroxymethylglutaryl-CoA reductase inhibitors, nephrectomy, disease progression, chemoprevention

Despite localized disease at initial treatment for renal cell carcinoma, approximately 10% of patients will have progression after surgery and the majority of those who do will die of the disease.[1–3] Currently there are no approved therapies to reduce the risk of recurrence, progression or death from RCC after the treatment of localized (N0M0) disease.

Statins have antineoplastic properties, including the ability to promote apoptosis, and inhibit inflammation, angiogenesis, cell proliferation,

0022-5347/14/1914-0914/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2013.10.141
Vol. 191, 914-919, April 2014
Printed in U.S.A.

migration/adhesion and invasion.[4–7] However, clinical evidence supporting an antineoplastic role for statins is encouraging but often conflicting.

The role of statins in RCC has not been studied thoroughly. Although laboratory evidence is encouraging,[8,9] only 3 clinical studies have examined the association between statins and RCC incidence.[10–12] A nested case-control study of nearly 500,000 veterans demonstrated that statin use was associated with a 48% reduction in the risk of RCC.[10] In a combination study of 2 large prospective cohorts, statin use was protective in women but not in men.[11] A third case-control study found no association.[12]

In the only laboratory study to examine statins and RCC progression, fluvastatin inhibited in vitro invasive properties and angiogenesis, and decreased progression of Renca xenografts to lung metastases in mice.[9] To date, no human study has explored the influence of statins on RCC progression. We examined the relationship between statins and progression after surgery for localized (N0M0) RCC.

MATERIALS AND METHODS

Study Population

With institutional review board approval we identified 2,608 patients with localized (N0M0) RCC treated with partial or radical nephrectomy between 1995 and 2010 at Memorial Sloan-Kettering Cancer Center. Patients treated earlier were excluded from analysis as statin use was rare at that time. Patients with known familial RCC syndromes were also excluded from study to reduce heterogeneity.

Medical records were reviewed, and detailed information on statin initiation and cessation, type, dose and duration was collected. Fuhrman grade was not routinely assigned for nonclear cell histology. Clinical stage was not available for all patients and, thus, was not used in this analysis. However, pathological stage was available for all patients.

Followup

Followup consisted of clinical visits every 6 months with history, physical examination, comprehensive metabolic panel, abdominal computerized tomography or ultrasound, and chest x-ray or chest computerized tomography. After 3 recurrence-free years, followup was lengthened to yearly intervals. Local recurrence was considered if new growth was detected in the surgical bed more than 3 months after surgery. Contralateral second primary tumors were not counted as local recurrence. Progression was classified as metastases or death from RCC. The date of death was considered the date of progression for 34 patients who died of RCC before the documentation of metastases.

Statistical Analysis

The primary aim was to investigate the difference in probability of progression and overall mortality between patients who used statins and those who did not at surgery. Due to the high rate of death from other causes, competing risk regression was used to compare progression risk between statin users and nonusers at surgery with death from other causes as the competing risk. Differences in overall mortality were analyzed using the Cox proportional hazards model. The 2 outcomes were examined separately in models adjusted for demographic, clinical, preoperative and pathological variables known to be associated with statin use or progression and mortality, namely age (continuous), gender (male/female), black race (black/other), Charlson score (4 or greater vs less than 4), GFR (continuous), surgery year (continuous), symptom presentation (asymptomatic/local/distant symptoms) and T stage (T3 or greater vs less than T3). As Fuhrman grade was not available for nonclear cell histology, it was not used in multivariate models.

Separate subgroup analyses were performed to assess whether the effects of statins varied by type (atorvastatin, simvastatin and other) and dose (equivalents of less than 10 mg, 10 mg, more than 10 mg atorvastatin).[13] Missing statin types were excluded from the subgroup analysis on type. Additional subgroup analyses compared clear cell with nonclear cell histology and stage (greater than T2 vs T2 or less).

We planned a sensitivity analysis to evaluate whether statin use between surgery and followup is associated with progression and overall mortality. Statin use was entered as a time dependent covariate into the multivariate models for progression and overall mortality. Date of surgery was considered the statin start date for patients who started statins before surgery. Patients starting statins after surgery but before progression contributed person-time to the nonuser group until starting statins, when they contributed person-time to the statin group. Patients who stopped statin use before surgery were considered nonusers (21). To test whether the result from the sensitivity analysis was different from the main analysis we used a chi-square test for heterogeneity. Survival time was calculated from surgery. Statistical analyses were conducted using Stata® 12.

RESULTS

A total of 708 (27%) patients were on a statin at surgery. Among nonusers at surgery 204 (8%) subsequently started statins at a median of 3.9 years after surgery. Baseline demographic and clinical characteristics of statin users and nonusers are summarized in table 1, and statin type and dose distribution are shown in table 2. Statin users were older (66 vs 60 years), tended to have worse comorbidities (19% vs 10% Charlson score 4 or greater) and worse ASA® (American Society of Anesthesiologists) score (57% vs 33% class 3/4), and were more likely to undergo partial nephrectomy (64% vs 54%). Statin use was higher in patients treated in recent years. There were no large differences in pathological features between statin users and nonusers at surgery (table 3).