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Prognostic impact of preoperative statin use after radical nephroureterectomy for upper urinary tract urothelial carcinoma

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Purpose: The objective was to investigate the impact of statin use on prognosis after radical nephroureterectomy for upper urinary tract urothelial carcinoma (UTUC).

Materials and Methods: A retrospective review of medical records identified 277 patients who underwent radical nephroureterectomy for primary UTUC at Asan Medical Center between January 2006 and December 2011. Information on preoperative statin use was obtained from patient charts in an electronic database. We assessed the impact of statin use on recurrence-free survival (RFS), cancer-specific survival (CSS), and overall survival (OS).

Results: Of these 277 patients, 62 (22.4%) were taking statin medications. Compared to the statin nonusers, the statin users were older, had a higher body mass index, and had higher rates of cardiovascular disease and diabetes. The 5-year RFS rates of statin users and nonusers were 78.5% and 72.5%, respectively (p=0.528); the 5-year CSS rates were 85.6% and 77.7%, respectively (p=0.516); and the 5-year OS rates were 74.5% and 71.4%, respectively (p=0.945). In the multivariate analysis, statin use was not an independent prognostic factor for RFS (hazard ratio, 0.47; p=0.056), CSS (hazard ratio, 0.46; p=0.093), or OS (hazard ratio, 0.59; p=0.144) in patients who underwent radical nephroureterectomy for UTUC.

Conclusions: Statin use was not associated with improved RFS, CSS, or OS in the sample population of patients with UTUC.

Keywords: Carcinoma; Hydroxymethylglutaryl-CoA reductase inhibitors; Transitional cell carcinoma

INTRODUCTION

The frequency of upper urinary tract urothelial carcinoma (UTUC) is approximately 5% of urothelial malignancies and <10% of renal tumors [1]. This cancer can be treated by radical nephroureterectomy with excision of the bladder cuff, but treatment is often problematic owing to difficulties in early diagnosis, the high incidence of tumor recurrence, and poor prognostic outcomes [2]. Because systemic recurrences are common in this disease, it is reasonable to consider perioperative treatments that might reduce this risk. However, few studies have explored

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such perioperative treatments, including chemotherapy or radiation therapy, and these limited studies have yielded conflicting results.

Some potential perioperative agents that might confer chemoprotective effects are vitamin A, vitamin E, vitamin C, selenium, nonsteroidal anti-inflammatory drugs, isoflavone, and statins (hydroxymethylglutaryl-CoA-reductase inhibitors). Of these, statins have been used to treat high cholesterol in general owing to their efficacy and minimal side effects. Statins improve the blood lipid profile, treat a number of cardiovascular diseases, and specifically reduce mortality from coronary heart disease [3]. Although vascular secondary end points are the main clinical target of these agents, statins also affect other conditions. In particular, a growing body of evidence suggests that statins provide a chemoprotective advantage against many cancers [4,5], likely by arresting cell cycle progression, suppressing angiogenesis, inducing apoptosis, and inhibiting tumor growth and metastasis [6-8].

Currently, preclinical data show that statins induce cell cycle arrest and apoptosis and inhibit proliferation in human urothelial carcinoma cell lines [9]. Thus, statins may have an antineoplastic effect on urothelial carcinoma. However, the impact of statin use has been investigated mainly in patients with lower urinary tract carcinomas owing to the infrequency of UTUC. In previous studies, statin use showed conflicting effects on the prognosis of patients with lower UTUC [10-12], and only one multi-institutional study did not suggest an influence of statin therapy on UTUC prognosis [13]. However, these studies were limited by heterogeneous groups of patients and variable follow-up schedules according to each institution. Therefore, we assessed the impact of statins on oncologic outcomes in patients with UTUC after radical nephroureterectomy performed at a single center.

MATERIALS AND METHODS

1. Study population and data collection

The study protocol was approved by the Institutional Review Board. A review of the medical records of our single institute identified 291 patients with primary UTUC who underwent radical nephroureterectomy between January 2006 and December 2011. Patients who had previous or synchronous invasive bladder cancer, who had distant metastasis at diagnosis, or who had received neoadjuvant therapy were excluded. Three patients with concomitant invasive bladder cancer and 11 patients with distant metastasis at diagnosis were excluded from analysis. The study cohort consisted of 277 consecutive patients.

Each patient underwent a preoperative evaluation, which included blood tests, urine cytology, cystoscopy, chest x-ray, abdominopelvic computerized tomography, and a bone scan. Information regarding medication use (statin use), the presence of comorbid illnesses, smoking history, and alcohol intake history was obtained from the electronic database. Because of the retrospective nature of data collection, we were unable to obtain the duration of statin use because this information was not available in the charts. The anesthesiologists used the American Society of Anesthesiologists score prior to surgery to assess the ability of patients to undergo surgery [14].

2. Pathological evaluation

In all cases, surgery was performed with curative intent. Radical nephroureterectomy with bladder cuff excision was performed and lymphadenectomy was performed when enlarged lymph nodes were either identified on preoperative computed tomography or were palpable during surgery. Dissection of the regional lymph nodes was performed in 101 patients (36.5%). Tumors were pathologically staged by using the 2010 American Joint Committee on Cancer TNM staging system, and tumors were graded according to the 2004 World Health Organization classification [15,16]. Lymphovascular invasion was defined as the presence of tumor cells within an endothelium-lined space without underlying muscular walls [17]. Adjuvant therapy was selectively recommended for patients with locally advanced or node-positive disease on pathology, except for those who could not tolerate chemotherapy of refused treatment. Adjuvant therapy was administered to 42 patients (12.3%), including 31 who received adjuvant chemotherapy and 27 who received adjuvant radiation therapy.

3. Follow-up

Follow-up consisted of chest radiography and abdominopelvic computed tomography every 6 months for the first 2 years and annually thereafter. Surveillance cystoscopy was generally performed every 3 months for the first 2 years after radical nephroureterectomy, every 6 months for the next 2 years, and annually thereafter. Tumor recurrence was defined as local failure in the tumor bed or regional lymph nodes or distant metastasis. Since bladder recurrence did not affect survival in the current patient population, this factor was not considered when calculating the RFS rate. The cause of death was determined by chart review and was corroborated by death certificates. All patients who died of cancer also had previous disease recurrence.

4. Statistical analysis

The statin user and nonuser subgroups were compared in terms of clinicopathological factors by using Pearson chi-square test or Fisher exact test for categorical variables and Student t-test or Mann Whitney U-test for continuous variables. Kaplan-Meier survival curves were used to estimate RFS and CSS and were compared by using the log-rank test. A Cox proportional hazards regression model was used to estimate the prognostic significance of each variable. Correlations between outcomes and variables were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). All statistical tests were two-tailed, with $p<0.05$ considered to be significant. All statistical analyses were performed by using the IBM SPSS Statistics ver. 21.0 (IBM Co., Armonk, NY, USA).

RESULTS

1. Baseline characteristics of the statin user and nonuser groups

Of the 277 patients, 62 (22.4%) reported being on statins at the time of radical nephroureterectomy, whereas 215

Table 1. Baseline clinicopathologic characteristics of patients in the statin use and nonuse groups

Variable	Statin user (n=62)	Statin nonuser (n=215)	p-value
Age (y)	66.8±8.8	62.7±10.4	0.006
Body mass index (kg/m^2)	25.6±3.7	24.5±3.2	0.015
Gender			0.738
Male	46 (74.2)	164 (76.3)	
Female	16 (25.8)	51 (23.7)	
Cardiovascular disease	17 (27.4)	33 (15.3)	0.039
Hypertension	31 (50.0)	83 (38.6)	0.143
Diabetes	20 (32.3)	32 (14.9)	0.003
ASA scores			0.190
1	5 (8.1)	24 (11.2)	
2	56 (90.3)	184 (85.6)	
3	1 (1.6)	7 (3.2)	
Smoking history			0.660
Current smoker	6 (9.7)	28 (13.0)	
Nonsmoker	56 (90.3)	187 (87.0)	
Bladder cancer history			1.000
Yes	11 (17.7)	37 (17.2)	
No	51 (82.3)	178 (82.8)	
Tumor location			1.000
Renal pelvis	26 (41.9)	89 (41.4)	
Ureter	36 (58.1)	126 (58.6)	
Pathologic T stage			0.284
≤T1	25 (40.3)	100 (46.5)	
T2	9 (14.6)	38 (17.7)	
T3	25 (40.3)	74 (34.4)	
T4	3 (4.8)	3 (1.4)	
Pathologic grade			0.473
Low	25 (40.3)	98 (45.6)	
High	37 (59.7)	117 (54.4)	
Lymph node status			1.000
N0 or Nx	57 (91.9)	197 (91.6)	
N1-3	5 (8.1)	18 (8.4)	
Lymphovascular invasion	23 (37.1)	55 (25.6)	0.080
Positive surgical margin	5 (7.9)	17 (7.9)	1.000
Adjuvant therapy	14 (22.6)	28 (13.0)	0.072

Values are presented as mean±standard deviation or number (%).
ASA, American Society of Anesthesiologists.

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were not. The statins used were lipophilic (n=57, 91.9%) and hydrophilic (n=5, 8.1%). The baseline clinicopathological characteristics of the patients are shown in Table 1. The two groups differed significantly in terms of age, body mass index (BMI), cardiovascular disease, and diabetes status. Compared to the statin nonusers, the statin users were older (66.8±8.8 years vs. 62.7±10.4 years, p=0.006), had higher BMIs (25.6±3.7 kg/m^2 vs. 24.5±3.2 kg/m^2, p=0.015), and had higher rates of cardiovascular disease (27.4% vs. 15.3%, p=0.039) and diabetes (32.3% vs. 14.9%, p=0.003). There were no significant differences in tumor stage, grade, lymphovascular disease, surgical margin status, or adjuvant therapy rate between the two groups.

2. Impact of statin use on cancer recurrence and mortality

At a median follow-up time of 40 months, 58 patients (18.8%) had disease recurrence and 42 patients (15.2%) had already died from UTUC progression. Of the patients who had died, 7 (11.3%) were statin users and 35 (16.3%) were statin nonusers. The 5-year RFS rates of statin users and nonusers were 78.5% and 72.5%, respectively (p=0.528) (Fig. 1A), and the 5-year CSS rates were 85.6% and 77.7%, respectively (p=0.516) (Fig. 1B). The 5-year OS rates were 74.5% and 71.4%, respectively (p=0.945) (Fig. 1C). Limiting the analysis to lipophilic statin agents only (i.e., rosuvastatin was excluded) also had no significant effect on outcomes (data not shown).

Table 2 presents the results of the univariate and multivariate analyses of RFS and CSS. Multivariate analysis revealed that the only statistically significant predictors of RFS and CSS were tumor grade, tumor stage, and adjuvant therapy. However, statin use (HR, 0.47; 95% CI, 0.22–1.02; p=0.056) was not an independent prognostic factor for RFS (HR, 0.47; 95% CI, 0.22–1.02; p=0.056) and CSS (HR, 0.46; 95% CI, 0.18-1.14; p=0.093).

In the multivariate analysis of prognostic factors for OS (data not shown), age (HR, 1.05; 95% CI, 1.02–1.07; p<0.001), tumor grade (HR, 1.97; 95% CI, 1.21–3.23; p=0.008), tumor stage (HR, 2.03; 95% CI, 1.20–3.42; p=0.001), surgical margin (HR, 2.12; 95% CI, 1.16–3.86; p=0.014), and lymph node status (HR, 2.39; 95% CI, 1.34–4.26; p=0.003) were independent

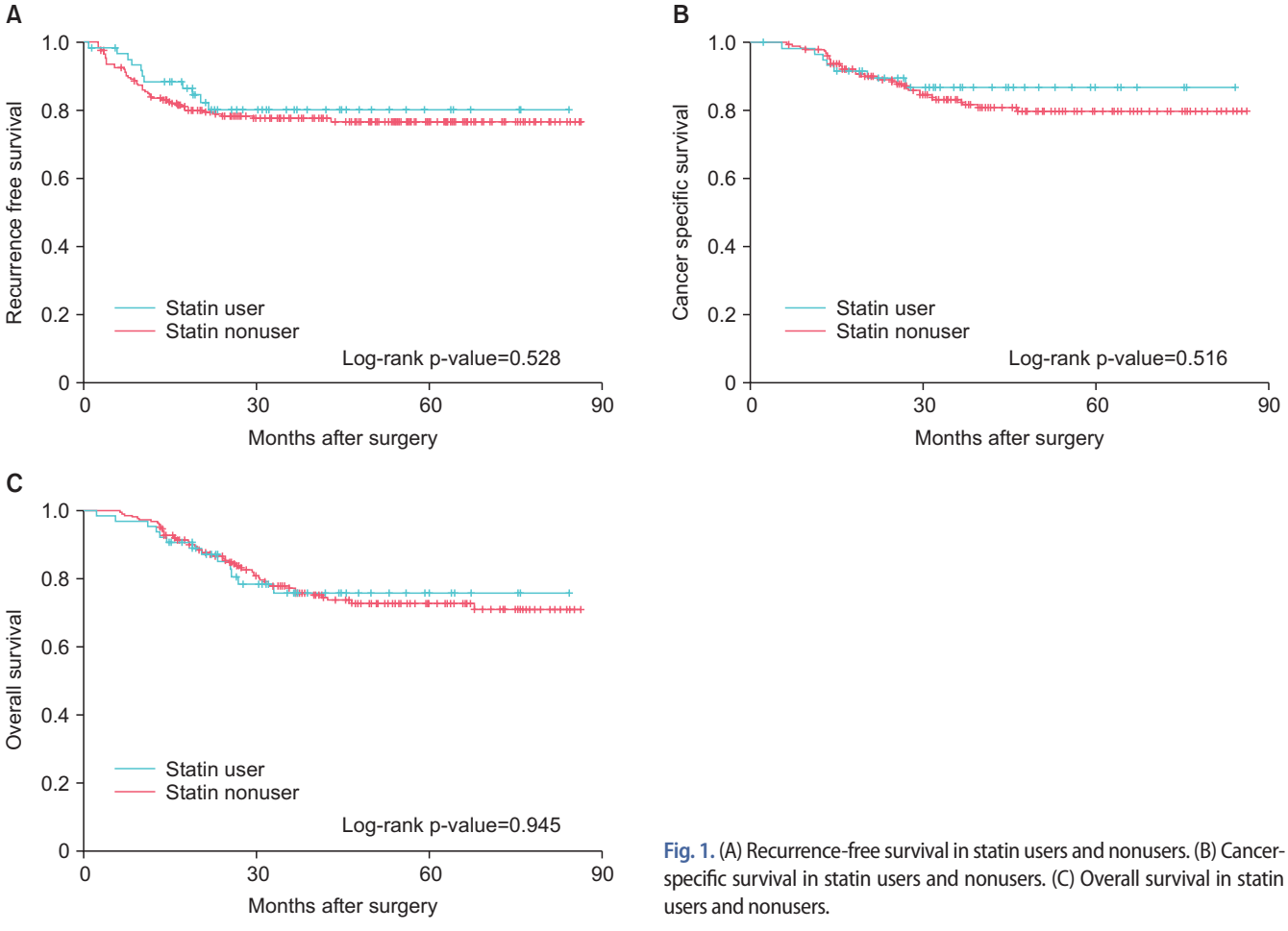

Fig. 1. (A) Recurrence-free survival in statin users and nonusers. (B) Cancer-specific survival in statin users and nonusers. (C) Overall survival in statin users and nonusers.

Table 2. Univariate and multivariate analysis of prognostic factors for recurrence (except bladder recurrence) and cancer-specific survival

Variable	Recurrence-free survival				Cancer-specific survival			
	Univariate		Multivariate		Univariate		Multivariate	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Age	1.12 (0.98–1.04)	0.434			1.02 (0.98–1.05)	0.335		
Body mass index	0.96 (0.88–1.05)	0.397			0.98 (0.89–1.08)	0.715		
Statin use								
No	1		1		1		1	
Yes	0.95 (0.45–1.97)	0.886	0.47 (0.22–1.02)	0.056	0.83 (0.34–1.99)	0.676	0.46 (0.18–1.14)	0.093
Tumor location								
Pelvis	1		-		1		-	
Ureter	1.33 (0.73–2.41)	0.348	-	-	1.53 (0.78–3.01)	0.219	-	-
Tumor grade								
Low	1		1		1		1	
High	6.25 (2.64–14.80)	<0.001	3.79 (1.53–9.35)	0.004	7.71 (2.72–21.86)	<0.001	4.45 (1.48–13.34)	0.008
Tumor stage								
≤T2	1		1		1		1	
≥T3	5.67 (2.39–13.43)	<0.001	3.31 (1.57–6.96)	0.002	5.15 (2.47–10.74)	<0.001	2.51 (1.07–5.87)	0.034
Node status								
pN0 or pNx	1		-		1		-	
pN1-3	2.72 (1.21–6.10)	0.016	1.31 (0.55–3.11)	0.540	3.71 (1.62–8.52)	0.002	1.92 (0.78–4.05)	0.154
LVI								
No	1		1		1		1	
Yes	2.57 (1.42–4.67)	0.002	1.28 (0.67–2.45)	0.459	3.39 (1.75–6.60)	<0.001	1.63 (0.77–3.43)	0.198
Surgical margin								
Negative	1		1		1		1	
Positive	3.58 (1.51–8.51)	0.004	1.87 (0.76–4.58)	0.172	4.76 (1.96–11.55)	0.001	2.44 (0.94–6.29)	0.066
Adjuvant therapy								
No	1		-		1		-	
Yes	5.36 (2.89–9.95)	<0.001	2.39 (1.19–4.80)	0.015	6.22 (3.15–12.30)	<0.001	2.47 (1.09–5.63)	0.031

CI, confidence interval; LVI, lymphovascular invasion.

prognostic factors for OS in patients who underwent radical nephroureterectomy for UTUC.

DISCUSSION

Currently, statins are being researched in a number of studies for their ability to prevent a variety of cancers, but the results have been inconsistent. One recent study showed that cancer patients who used statins prior to diagnosis had reduced CSS compared with that of patients who had never taken statins [5]. However, that study did not report on UTUC patients specifically and the effects of statin use on the clinical treatment outcomes of urothelial cell carcinoma are unknown.

Especially in urology, the effect of statins on prostate cancer incidence and disease progression has been investigated in many studies [18,19]. Recent meta-analysis showed a 33% risk reduction for advanced high-grade or metastatic prostate cancer [20] and that statin use protects against prostate cancer with poorer pathological characteristics [21]. In our previous study [22], we showed that postoperative statin use decreased the risk of biochemical recurrence, especially in patients with high-risk disease. However, only few studies have investigated the effect of statins on urothelial carcinoma incidence and prognosis. In one previous study that examined the effects of atorvastatin on human bladder cancer cell lines, a significant anti-proliferative effect was observed in the statin group compared with controls [9]. In another study using mouse cells transfected with the H-ras oncogene from human bladder carcinoma, the researchers observed that statin treatment significantly inhibited Ras oncogene-transformed cells [23]. Thus, statin may have an antineoplastic effect on urothelial carcinoma. However, these studies are preclinical data.

To date, only a few studies have focused their investi-

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gations on the clinical effect of statins on urothelial carcinoma incidence and prognosis, and these studies have primarily concentrated on bladder carcinoma, not UTUC. Tsai et al. [12] suggested that statins may improve local control in patients who underwent concurrent chemoradiotherapy for muscle-invasive bladder cancer. However, this study showed that statin use was associated with local control only in univariate, not multivariate, analysis. Recently, one multi-institutional study found that statin use was not associated with RFS or CSS in patients treated with radical nephroureterectomy for UTUC [13]. Similarly, statin use was also not associated with RFS or CSS in patients treated with radical cystectomy for bladder cancer, and statins did not affect the oncologic outcome for non–muscle-invasive bladder cancer [10,11]. Additionally, a recent meta-analysis study showed no significant association between statin use and the risk of bladder cancer [24]. Furthermore, there have been 5 retrospective studies exploring the impact of statin use on patient responses to Bacillus Calmette-Guerin (BCG) immunotherapy. Hoffmann et al. [25] reported that concurrent statin therapy with BCG might reduce the clinical efficacy of BCG therapy. Statin users were more likely to proceed to more aggressive disease as well as to require radical cystectomy. However, subsequent studies failed to confirm that statin therapy affects patient responses to BCG [11,26-28]. These studies found no differences between statin users and nonusers in the mean number of recurrences or incidence of disease progression, CSS, or OS. Overall, these results are consistent with the findings in our study, in which statin use did not improve RFS, CSS, or OS after radical nephroureterectomy for UTUC.

When interpreting our data, several noteworthy limitations should be considered. First, because the findings represent the clinical experience of a single center, the rate of patients taking statins was lower than in a previous study [13]. However, the prevalence of statin use in patients 50 years or older was 22.8% in 2008 [29]. Second, medical chart review can be an unreliable method for determining the duration and dosage of medications used by a study population, because much of this information may not be reported consistently in the medical records. It would be interesting to assess the correlation between the dosage and the duration of statin use with prognosis, but unfortunately, this information was not available in the patient records. Therefore, well-designed, prospective, randomized trials that include a large patient population are warranted. Despite the limitations of the present study, to the best of our knowledge, this is the first single-center study to investigate the potential impact of statin use on the clinical outcomes of patients with UTUC being treated with radical nephroureterectomy.

CONCLUSIONS

In patients undergoing radical nephroureterectomy for UTUC, statin use was not associated with RFS, CSS, or OS. Owing to the inherent limitations of this retrospective study, the potential antineoplastic effect of statins needs further investigation prospectively.

CONFLICTS OF INTEREST

The authors have nothing to disclosure.

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