An Analysis of the Effect of Statin Use on the Efficacy of Bacillus Calmette-Guerin Treatment for Transitional Cell Carcinoma of the Bladder

Ryan K. Berglund,* Caroline J. Savage, Kinjal C. Vora, Jordan M. Kurta and Angel M. Cronin

From the Division of Urology, Memorial Sloan-Kettering Cancer Center, New York, New York

Purpose: Bacillus Calmette-Guerin is an effective immunotherapy for carcinoma in situ of the bladder and it reduces recurrence from resected papillary transitional cell carcinoma of the bladder. Many patients receiving bacillus Calmette-Guerin therapy are concurrently taking statin agents, which have known immunomodulatory properties and may alter the performance of bacillus Calmette-Guerin. Some data have suggested that patients taking a statin while on bacillus Calmette-Guerin therapy experience reduced clinical efficacy.

Materials and Methods: We conducted a retrospective review of 952 consecutive patients from 1978 through 2006. Time to recurrence and progression to surgery were compared between those taking and those not taking a statin by Kaplan-Meier methods and multivariable Cox regression controlling for stage and grade.

Results: There were 245 (26%) patients taking a statin before bacillus Calmette-Guerin therapy and 707 not on statin therapy (74%). A total of 796 patients had recurrence overall with 214 in the statin group and 582 in the other group. Median time to recurrence was similar between those who did and those who did not use a statin. On multivariable analysis statin use was not significantly associated with recurrence (hazard ratio 1.04; 95% CI 0.81, 1.34; $p = 0.7$) or progression to surgery (hazard ratio 0.77; 95% CI 0.52, 1.13; $p = 0.17$) after bacillus Calmette-Guerin therapy.

Conclusions: This retrospective study in a large cohort of patients showed no statistically significant association between statin use and recurrence or progression to open surgery in patients treated with bacillus Calmette-Guerin for transitional cell carcinoma of the bladder. Based on these data patients should not be discouraged from taking statins while undergoing bacillus Calmette-Guerin treatment.

Key Words: carcinoma, transitional cell; mycobacterium bovis; immunotherapy

Bacillus Calmette-Guerin is an effective intravesical therapy for superficial TCC of the bladder and has been used for more than 30 years.[1] As an induction and maintenance treatment for resected superficial TCC (Tis, Ta and T1 disease) it has been proven to reduce recurrence and progression of disease as well as improve survival.[2,3] In fact, it is regarded as the gold standard immunotherapy adjunct to resection which has been proven superior to intravesical chemotherapy in a prospective randomized trial.[4]

Many patients with superficial TCC have concurrent hyperlipidemia, hypercholesterolemia and atherosclerotic disease. HMG-CoA reductase inhibitors, or statins, are the most common first line therapy for these conditions and they are used by more than 25 million people worldwide on a daily basis. Statins also have known immunomodulatory properties and they are being actively studied in the treatment of autoimmune disease.[5]

It has recently been suggested that these immunomodulatory properties may reduce the efficacy of intravesical BCG therapy if statins are taken concurrently. A small retrospective series showed an increased rate of progression of disease and progression to open surgery in patients on statins compared to those who were not on statins.[6] However, this finding was not confirmed in a larger retrospective series published by another group.[7] Currently these groups disagree as to whether a recommendation should be made against the use of statins while undergoing BCG therapy.

At our institution all patient outcomes from BCG treatment have been collected in a prospective database since 1978 and statin therapy has been available since the mid 1980s. In our study we compare the recurrence and progression outcomes of patients on BCG therapy who are receiving statins compared to those who are not on statins to determine if there is a difference in cancer specific outcomes.

MATERIALS AND METHODS

From July 1978 until November 2006, 1,218 patients were treated with induction BCG therapy at our institution. Of these patients 253 were eliminated from analysis for missing prior TUR data for staging and grading, and 13 were eliminated for having received prior surgical intervention, leaving a total of 952 patients for analysis. Patients were evaluated with an office visit, physical examination, urine cytology and repeat office cystoscopy every 3 months for 1 year after the initial TUR and BCG treatment. Followup was then on a semiannual basis. Recurrence was defined as visual and/or biopsy proven evidence of recurrence at cystoscopy or a positive repeat cytol-

Submitted for publication February 8, 2008.

* Correspondence: Division of Urology, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, New York 10021 (telephone: 212-639-2000; e-mail: berglunr@mskcc.org).

DOI:10.1016/j.juro.2008.06.034

TABLE 1. *Patient characteristics before BCG treatment*

	Used Statins Before BCG			
	No		Yes	
Mean age at BCG treatment (range)	65 (57, 72)		69 (62, 75)	
No. gender (%):				
Male	550	(78)	209	(85)
Female	157	(22)	36	(15)
No. pre-BCG stage (%):				
Ta/T1/TIS	376	(53)	123	(50)
T2/T3	33	(5)	5	(2)
Unknown	298	(42)	117	(48)
No. pre-BCG grade (%):				
Low	90	(13)	18	(7)
High	320	(45)	127	(52)
Unknown	297	(42)	100	(41)

ogy. Open surgical intervention was discussed with patients at the primary visit if they had pathological stage T1 or greater disease. Patients with recurrent multifocal and/or high grade disease were offered cystectomy at the initial recurrence.

We evaluated 2 separate time to event outcomes after initial BCG therapy, that is recurrence and progression to open surgery. The event-free probabilities stratified by statin use before BCG therapy were estimated using Kaplan-Meier methods and were compared using the log rank test. Multivariable analyses to evaluate the association between statin use and the events, controlling for pre-BCG stage (categorized as Ta/T1/TIS and T2/T3) and grade (categorized as high and low), were done using Cox proportional hazards regression. The covariates in the multivariable analysis were specified before any data analysis and instances of missing data were excluded from multivariable analysis. Statistical analyses were conducted using Stata® 9.2.

RESULTS

Pretreatment patient characteristics are shown in table 1. Approximately a quarter of the patients (245) used statins. Patients who used statins tended to be older (median 69 vs 65 years) and were more likely to be male (85% vs 78%) than those who did not use statins. Clinical stage was similar between these groups although a higher proportion of patients who used statins had high grade disease (52% vs 45%).

Overall 796 patients had recurrence, of whom 214 used statins and 582 did not. Median followup for patients who did not have disease relapse was 4.3 years. The recurrence-free probabilities by statin use were similar. For example, median time to recurrence was 9 months for patients with and without statin use (fig. 1, $p = 0.13$). On multivariable analysis we saw no evidence that stain use was associated with recurrence after BCG therapy (hazard ratio 1.04; 95% CI 0.81, 1.34; $p = 0.7$).

There were 365 patients who underwent open surgery following BCG therapy, of whom 78 did and 287 did not use statins. Median followup for those who did not undergo open surgery was 3.8 years. Patients who used statins had a slightly shorter median time to open surgery (11 vs 9 years, fig. 2, $p = 0.13$). On multivariable analysis statin use was not significantly associated with open surgery after BCG treatment (hazard ratio 0.77; 95% CI 0.52, 1.13; $p = 0.17$). Overall stage, grade and statin use had no statistically significant effect on relapse-free survival or progression to open surgery (table 2).

As a sensitivity analysis we repeated our analysis in the subset of 890 patients treated after 1990, which represents a contemporary cohort. On multivariable analysis the hazard ratio associated with statin use for the outcome of subsequent recurrence was 1.02 ($p = 0.9$) and for the outcome of open surgery it was 0.73 ($p = 0.10$). These key statistics were similar to those obtained in the entire cohort. Therefore, we conclude that our results were not affected by the inclusion of patients treated before 1990.

DISCUSSION

In the present study there was no statistically significant difference in recurrence or progression to surgery between patients taking and not taking statins, and this was confirmed on multivariable analysis. In fact, this study shows that most patients regardless of statin use will have recur-

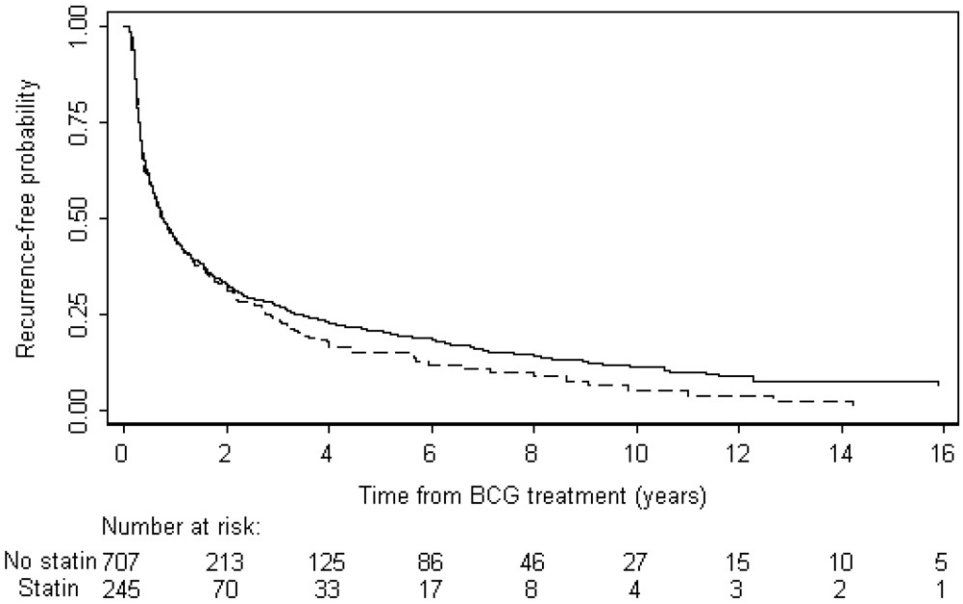

FIG. 1. Kaplan-Meier recurrence-free probability following BCG therapy stratified by statin use. Solid line indicates no statin use. Broken line indicates statin use.