ELSEVIER

CrossMark

BRACHYTHERAPY

Brachytherapy 14 (2015) 179–184

Statin use not associated with improved outcomes in patients treated with brachytherapy for prostate cancer

John Cuaron[1], Xin Pei[1], Gil'ad N. Cohen[1,2], Brett W. Cox[1], Yoshiya Yamada[1], Michael J. Zelefsky[1], Marisa A. Kollmeier[1,*]

[1]*Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY*
[2]*Department of Medical Physics, Memorial Sloan Kettering Cancer Center, New York, NY*

ABSTRACT

PURPOSE: To investigate the association between statin use and prostate cancer outcomes in intermediate- and high-risk patients treated with brachytherapy for prostate cancer.

METHODS AND MATERIALS: Between 1998 and 2010, 754 men with National Comprehensive Cancer Network intermediate- ($n = 627$) and high-risk ($n = 127$) prostate cancer were treated with prostate brachytherapy at our institution. Patients received either low-dose-rate or high-dose-rate brachytherapy as monotherapy or in combination with supplemental external beam radiotherapy. Two hundred eighty-five patients (37.8%) also received androgen-deprivation therapy. Two hundred seventy-three men (36.2%) were identified as taking statin medication before initiating radiation therapy. Prostate-specific antigen relapse–free survival (PSA-RFS), distant metastasis–free survival (DMFS), and overall survival were compared using log-rank tests. Associations of patient and treatment characteristics with outcomes were analyzed with univariate and multivariate regression. The median followup was 48 months.

RESULTS: The 8-year PSA-RFS for intermediate-risk, high-risk, and all patients was 92.2%, 64.1%, and 87.7%, respectively. The 8-year DMFS was 97.1%, 82.9%, and 94.9%, respectively. The 8-year overall survival for the entire cohort was 86.6%. There were no significant differences between statin users and nonusers when stratified by risk group, nor when analyzed as a full cohort. On multivariate analysis, Gleason score $4 + 3 = 7$ and >7 were significantly associated with worse PSA-RFS ($p \leq 0.003$ and <0.001, respectively). Gleason score > 7 ($p = 0.008$) and the use of neoadjuvant androgen-deprivation therapy ($p = 0.03$) was associated with worse DMFS. Statin use did not significantly impact PSA-RFS or DMFS.

CONCLUSIONS: Pretreatment statin use is not associated with improved outcomes in intermediate- and high-risk patients undergoing prostate brachytherapy-based regimens for prostate cancer.

Keywords: Statins; Brachytherapy; Prostate cancer

Introduction

3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, also known as statins, have gained widespread use for their lipid-lowering properties and significant reduction in risk of coronary artery disease and mortality (1). While statins prevent the synthesis of cholesterol in the liver by competitively inhibiting the enzyme 3-Hydroxy-3-methylglutaryl coenzyme A-reductase, they have also demonstrated potential anticancer activity, including the ability to decrease cell proliferation by downregulation of the androgen receptor in prostate cancer cells (2).

Studies investigating the effects of statins on prostate cancer diagnosis and treatment outcomes have yielded mixed results. Associations between statin use and a decreased risk of advanced prostate cancer (3) have been described. Although some series have shown a decreased risk of biochemical failure after radical prostatectomy (4) and radiation therapy (RT) (5–7) with statin use, others have shown no significant benefit (8, 9). To further investigate the effect

Received 25 March 2014; received in revised form 27 May 2014; accepted 28 May 2014.

Conflict of interest: The authors have no financial disclosures or conflicts of interest to disclose.

* Corresponding author. Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065. Tel.: +1-212-639-3952; fax: +1-212-717-3104.

E-mail address: mkollmeier@mskcc.org (M.A. Kollmeier).

1538-4721/$ - see front matter
http://dx.doi.org/10.1016/j.brachy.2014.05.019

of statin therapy on brachytherapy for prostate cancer, we examined the association between statin use and biochemical and clinical outcomes in intermediate- and high-risk patients treated with brachytherapy-based regimens for prostate cancer. We chose to focus on intermediate- and high-risk patients because of the relatively small percentage of these patients represented in previous studies. We also hypothesized that differences among statin users and nonusers would be more evident among intermediate- and high-risk patients, given the historically excellent rates of biochemical control among low-risk patients treated with brachytherapy.

Methods

Between 1998 and 2010, a total of 1655 patients with clinically localized prostate cancer were treated with prostate brachytherapy with or without external beam RT (EBRT) at our institution. Of those patients, 754 men with National Comprehensive Cancer Network (NCCN) intermediate- ($n = 627$) and high-risk ($n = 127$) prostate cancer were included in this analysis. Patients received either low-dose-rate (LDR; $n = 217$) or high-dose-rate (HDR; $n = 12$) monotherapy (median dose, 144 and 38 Gy, respectively) or LDR ($n = 327$; median dose, 110 Gy) or HDR ($n = 198$; median dose, 19.5 Gy) in combination with supplemental EBRT (median EBRT dose, 50.4 Gy). For the 544 patients receiving LDR, 397 patients received ^{125}I and 147 patients received ^{103}Pd. Two hundred eight-five patients (37.8%) also received androgen-deprivation therapy, typically beginning 2–3 months before and concurrent with radiotherapy.

All patients had medication information available at initial consultation. We identified a total of 273 men (36.2%) who were taking a statin medication (statin group) before initiating RT. The clinical characteristics of the statin and the nonstatin group are summarized in Table 1.

Our techniques of LDR and HDR brachytherapy have been previously described (10, 11). All brachytherapy procedures were performed using real-time transrectal ultrasound-guidance in the dorsal lithotomy position under general anesthesia. For LDR brachytherapy, an intraoperative planning system that incorporates a genetic optimization algorithm was used to achieve the optimal seed-loading pattern for delivery of the prescription dose of 144 Gy for monotherapy. For combined modality regimens, a dose of 110 Gy using ^{125}I or 100 Gy using ^{103}Pd was delivered. A Day 0 postimplant CT was performed for postimplant dosimetry analysis. For HDR brachytherapy, all patients were treated with ^{192}Ir using a Gammamed 12i delivery unit (Varian Medical Systems, Inc., Palo Alto, CA) with dosimetric evaluation performed using an in-house CT-based treatment-planning system incorporating genetic optimization. Patients were treated with three fractions delivered 4–6 h apart during an overnight hospital stay. For 525 (69.6%) patients who received supplemental EBRT, this was typically delivered 4–8 weeks after the brachytherapy procedure. Five to seven fields were used to deliver 45–60.2 Gy (median dose, 50.4 Gy) with urethral-sparing optimization.

Table 1
Baseline clinical and treatment characteristics of entire patient cohort

Characteristics	No statins, $N = 481$ [n (%)]	Statins, $N = 273$ [n (%)]	p-Value
Age			
<65	192 (40)	77 (28)	0.002
≥65	289 (60)	196 (72)	
PSA			
<10	342 (71)	221 (81)	0.01
10–20	125 (26)	42 (15)	
>20	14 (3)	7 (3)	
T stage			
T1–T2a	359 (75)	216 (79)	0.08
T2b–T2c	93 (19)	50 (18)	
T3a+	29 (6)	7 (3)	
Gleason score			
<7	77 (16)	43 (16)	0.52
3 + 4 = 7	258 (54)	159 (58)	
4 + 3 = 7	81 (17)	43 (16)	
>7	65 (14)	28 (10)	
NCCN Risk Group			
2	390 (81)	237 (87)	0.043
3	91 (19)	36 (13)	
Neoadjuvant HT			
Yes	192 (40)	93 (34)	0.78
No	289 (60)	180 (66)	
EBRT			
Yes	341 (71)	184 (67)	0.32
No	140 (29)	89 (33)	

PSA = prostate-specific antigen; NCCN = National Comprehensive Cancer Network; HT = hormone therapy; EBRT = external beam radiotherapy.

In general, posttreatment followup was performed every 6 months for the first 3 years and annually thereafter. The median followup for the entire cohort was 48 months (range, 1–156 months). A prostate-specific antigen (PSA) relapse was defined using the Phoenix nadir + 2 definition. Distant metastases were defined as clinical or radiographic evidence of disease outside the pelvis.

PSA relapse–free survival (PSA-RFS) was defined from the date of the end of all RT to the date of PSA relapse. Distant metastasis–free survival (DMFS) was defined from the date of the end of RT to the date of first report of distant metastasis. For these endpoints, patients were censored at the time of last followup or at the time of death from any cause. Overall survival (OS) was defined from the date of the end of RT to the date of death from any cause, and patients were censored at the time of last followup. PSA-RFS, DMFS, and OS curves were generated using the Kaplan-Meier method and outcomes between the statin-user and nonuser groups were compared using log-rank tests. Univariate and multivariate analysis was performed to determine associations of statin use, neoadjuvant hormonal therapy use, Gleason score (GS), use of combination therapy,