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ASPIRIN AND STATIN NON-USE ASSOCIATED WITH EARLY BIOCHEMICAL FAILURE FOLLOWING PROSTATE RADIOTHERAPY

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Abstract

PURPOSE—To present the largest retrospective series investigating the effect of aspirin and statins, which are hypothesized to have anti-neoplastic properties, on biochemical failure (BF, Nadir+2) following prostate radiotherapy (RT).

METHODS AND MATERIALS—Between 1989 and 2006, 2051 men with clinical localized prostate cancer received definitive RT alone (median dose: 76 Gy). Aspirin or statin use (defined as any use at the time of RT or during follow-up) was 36% and 34%, respectively. The primary endpoint of the study an interval to BF (IBF) < 18, which has been shown to be the single strongest predictor of distant metastasis, prostate cancer survival, and overall survival following RT. Patient demographic characteristics and tumor staging factors were assessed in regard of associations with the endpoint. Univariate analysis was performed using the Chi-square test for categorical variables and the Wilcoxon test for continuous variables. Multivariable analysis was done via a multiple logistic regression.

RESULTS—The median follow-up was 75 months. Univariately, IBF < 18 months was associated with aspirin non-use ($p < 0.0001$), statin non-use ($p < 0.0001$), anticoagulant non-use ($p = 0.0006$), cardiovascular disease ($p = 0.0008$), and PSA (continuous, $p = 0.008$); but, not Gleason score, age, RT dose, or T-stage. On multivariate analysis, only aspirin non-use ($p = 0.0012$, OR=2.052, CI:1.328–3.172) and statin non-use ($p = 0.0002$, OR=2.465, CI: 1.529–3.974) were associated with IBF < 18 months.

CONCLUSIONS—In patients who received RT for prostate cancer, aspirin or statin non-use was associated with early BF, a harbinger of distant metastasis and death. Further study is needed to confirm these findings and to determine the optimal dosing, schedule, as well as the relative benefits and risks of both therapies in combination with RT.

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Keywords

Radiotherapy; prostate cancer; aspirin; statin

INTRODUCTION

Aspirin is one of the most widely used medicines in the world.(1) In the 1950s Dr. Lawrence Craven suggested that the mild anticoagulant properties of aspirin might be useful for the prophylaxis of thrombosis and embolism.(2) It was not long after the anti-platelet and fibrinolytic properties of aspirin were found to inhibit the spread of cancer in laboratory studies. (3). Statins, first used around 1980 as treatment for hypercholesterolemia, similarly have had promising antineoplastic potential since their effect to affect the G1 phase of tumor and normal cell cycles was shown in the early 1990s. (4)

However, there are few clinical studies that examine the effect of either drug on cancer. A recent secondary analysis of 25,570 patients from eight randomized clinical trials of aspirin versus control (done originally for primary or secondary prevention of vascular events) indicate that aspirin use reduces the risk of death from gastrointestinal cancers, adenocarcinomas of the lung, and primary brain tumors.(5) With regard to prostate cancer, there was a trend toward a statistically significant reduction in the incidence of prostate cancer ($p = 0.09$) associated with aspirin use versus non-use in a subset of 5085 men treated on the Thrombosis Prevention Trial. Similarly, there was a similar trend for improvement in disease specific survival with aspirin use (hazard ratio = 0.81; 95% confidence interval = 0.61 – 1.06, $p = 0.12$) in the 10,502 patients with more than 5 years' scheduled duration of trial treatment and long-term follow-up. These results suggest that aspirin may have a role in either preventing the development of prostate cancer or improving the effectiveness of treatment.

Reports specifically studying the effects of aspirin on prostate cancer treatment are lacking. Anti-coagulants and aspirin were investigated in combination with radiotherapy by Choe et al.(6) The authors retrospectively compared 662 clinically localized prostate cancer patients based on anticoagulant use and found both the four-year rate of biochemical failure (BF, 9% vs. 22%, $p = 0.0002$) and distant metastasis (DM, 1% vs. 5%, $p = 0.03$) were significantly improved with anticoagulant use.

In comparison, the success of statins *in vitro* has led to a number of phase I and I/II oncologic clinical trials for various cancers including prostate cancer.(7, 8) Tan et al. (8) found that men diagnosed with prostate cancer on statins were less likely to have digital rectal examination positivity, Gleason score 7 or greater prostate cancer, and high volume prostate cancer when compared to those not taking statins. In another study,(9) 387 men who died from prostate cancer were matched to controls. Medication data were obtained identically for cases and controls. Statin use was associated with an unadjusted odds ratio (OR) of 0.49 (95% confidence interval [CI] = 0.34 – 0.70) and decreased to 0.37 ($P < .0001$) after adjusting for education, waist size, body mass index, comorbidities, and antihypertensive medication. These results give further promise to the potential beneficial effects of statin therapy.

In this report we set forth to examine the effect of aspirin and statin use on biochemical failure (BF) in men treated definitively with external beam RT. To our knowledge, this is the largest study examining the use of either drug in prostate cancer patients treated with a single modality.

MATERIALS AND METHODS

Between 1989 and 2006, 2,051 men with clinical Stage T1–4, N0/X, M0 adenocarcinoma of the prostate received definitive RT without androgen deprivation therapy. Of the 2,051 patients, 1,305 (64%) were treated with 3D-conformal RT (3D-CRT, July 1992 to June 2001) and 746 (36%) with intensity modulated radiation therapy (IMRT, July 2001 to July 2006). The median follow-up time from completion of RT was 75 months (range, 18–239). All patients provided informed consents for participation in a database study approved by the institutional review board.

Radiotherapy

The techniques used for 3D-CRT and IMRT have been previously reported.(10, 11) Briefly, patients were immobilized supine in a thermoplastic cast and daily prostate localization was performed in all patients using either the B-type acquisition ultrasound, fiducial markers with electronic portal, computed tomography imaging, or radiofrequency beacons. The planning target volume included the prostate and 1 cm margin for 3D-CRT and 8 mm for IMRT, except posteriorly where the margin was less to enable better rectal sparing. The RT dose was prescribed such that 95% of the planning target volume received 100% of the prescribed dose.

Patient evaluation and staging

All patients had a history and physical exam including digital rectal exam, initial serum PSA, and histologic confirmation of adenocarcinoma with a Gleason score (GS). Thirty percent of patients had computed tomography of the abdomen and pelvis while 86% had a bone scan to exclude metastasis. T-category was established by palpation findings only, without upstaging using pathologic or radiographic information. Aspirin and statin use were defined as use either at the time of RT or during follow-up. Stain drugs included atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin. Anticoagulant use was defined as use of warfarin at the time of RT or during follow-up. Cardiovascular disease was defined as any patient with a current or past history of myocardial infarction, coronary artery disease, coronary artery bypass grafting or stenting.

Statistical analysis

The primary endpoint of the study was an interval to BF (Nadir+2 ng/mL) < 18 months. An IBF < 18 months has been shown to be the single strongest predictor of distant metastasis, prostate cancer specific survival, and overall survival following prostate radiotherapy.(12–14) All patients were required to have a minimum 18 months follow-up. a binary variable of whether patients developed BF within 18 months after the start of RT. BF was defined as the nadir value PSA plus 2ng/mL. Patient demographic characteristics and tumor staging factors were assessed in regard of associations with the endpoint. Univariate analysis was performed using the Chi-square test for categorical variables and the Wilcoxon test for continuous variables. Multivariable analysis was done via a multiple logistic regression by including only those variables that were statistically significant in the univariate analysis. A p-value <0.05 was considered significant. All analyses were carried out with SAS 9.2.

RESULTS

Various patient- and treatment-related characteristics are listed in Table 1. The proportion of patients with low-, intermediate-, and high-risk disease based on National Comprehensive Cancer Network (NCCN) criteria were 45% (n = 917), 45% (n = 913), and 11% (n = 219), respectively. Thirty-six (n = 743) of men reported aspirin use: 21% (n=158) initially, 39% (n = 288) during follow-up, and 40% (n = 297) for both. Thirty-four percent (n = 691) of men

reported statin use: 9% initially (n = 63), 57% (n = 392) during follow-up, and 34% (n = 236) for both. Thirty-five (n = 711) percent of patients had cardiovascular disease.

Tables 2–5 present univariate analysis results. IBF < 18 months was associated with aspirin non-use (p<0.0001, Table 2), statin non-use (p<0.0001, Table 3), anticoagulant non-use (p=0.0006, Table 4), cardiovascular disease (p =0.0008, Table 5), and initial PSA (continuous, p=0.008). Similar univariate analyses showed that Gleason score (2–6 vs. 7 vs. 8–10), age (continuous), RT dose (continuous), and T-stage (1–2 vs. 3–4) were not significantly predictive of IBF < 18 months.

On multivariate analysis, aspirin non-use (p=0.0012) and statin non-use (p=0.0002) were associated with IBF < 18 months in a model including initial PSA, anticoagulant non-use, and cardiovascular disease. Aspirin non-use had an odds ratio (OR) of 2.052 for IBF < 18 months (95% confidence interval [95% CI] = 1.328 – 3.172) and statin non-use had an OR of 2.465 (95% CI = 1.529 – 3.974) (Table 6). OR estimates for initial PSA, use of an anticoagulant, or cardiac disease were not significant.

DISCUSSION

In this study, we investigated the impact of aspirin and statin use on BF following RT for prostate cancer. We demonstrated that men who were taking aspirin, statin, either at the initiation of RT or anytime during follow-up, were less likely to develop BF by 18 months, a harbinger of distant metastasis and death.(12–14) This effect was seen on multivariate analysis when we accounted for other factors, including use of any anticoagulant, presence of cardiovascular disease, Gleason score, initial PSA, and T-stage. Thus, the observed effect of aspirin and statins may be due to their anti-neoplastic effects.

Several mechanisms by which aspirin impedes cancer development have been proposed.(15) First, aspirin interferes with prostaglandin formation from arachidonic acid,(16) and prostaglandins have been shown to stimulate prostate cancer growth.(17) Arachidonic acid accumulation stimulates conversion of sphingomyelin to ceramide, which promotes apoptosis in colon cancer cells.(18) Second, aspirin is a cyclo-oxygenase-2 (COX-2) inhibitor that has been shown to suppress prostate tumor growth in human cell lines.(19) COX-2 is up-regulated in prostate cancer and overexpression correlates positively with higher tumor grade,(19) as well as BF and DM following RT.(20)

Aspirin has been shown to promote COX-independent apoptosis in cancer cells. COX-2 blockers increase expression of the pro-apoptotic Par-4 gene in prostate carcinoma cells.(21) Additionally, aspirin induces expression of pro-apoptotic proteins bax and bak in gastric carcinoma cells.(22) Bax translocates to mitochondria and causes cytochrome c release into the cytosol to promote HeLa cell apoptosis.(23) Salicylates have been shown to selectively activate p38 MAPK, resulting in induction of programmed cell death in human fibroblasts.(24) In fibrosarcoma cells, salicylates promote expression of the pro-apoptotic p53, p21, and bax; while concurrently downregulating anti-apoptotic Bcl-2 expression.(24) Finally, aspirin induces DNA fragmentation by caspase activation, which causes death of B-chronic lymphocytic leukemia cells.(25) These studies provide plausible biological mechanisms for our observation of a decrease in BF.

Statins, similarly, have been shown to have antineoplastic effects. Statins have been shown to trigger G1 arrest in some cells in vivo,(26) and multiple biochemical mechanisms of action have been proposed. Similar to aspirin, statins have been shown to mediate the arrest response of p21.(27) Statins uniquely affect fatty acid synthesis; and they have immunomodulatory effects, including apoptosis of CD4+ T cells, downregulation of

chemokine secretion and receptor expression, angiogenesis, cell proliferation, and suppression of adhesion molecules on organ tissue and circulating cells.

To date, our study is the largest retrospective series that specifically investigates aspirin and statin use in a population composed exclusively of prostate cancer patients receiving RT. Our results are consistent with other similar reports in the literature. Choe et al.,(6) who investigated anticoagulant therapy including aspirin, observed an improvement in BF following RT. Marcella et al. found that statin use was associated with substantial protection against prostate cancer death. (9). Our findings are similar to those of Alizadeh et al. (28) and Gutt et al., (29) who concluded that statin use results in better BF rates after RT, but had no influence on overall survival, cause-specific survival, or freedom from distant metastasis. This may also explain the findings of Rothwell et al. (5), who found that there was no statistical significance for an improvement in 20-year risk of death due to prostate cancer ($p = 0.12$) in a pooled analysis from eight randomized clinical trials of aspirin versus control done originally for primary or secondary prevention of vascular events.

It is important to note several potential limitations of this study. First, it is retrospective and observational in nature, so one can draw association but not causation between drug use and risk of BF. Second, aspirin and statin use were defined broadly. It is not possible to comment on the effect of the dosage, duration, or timing of aspirin or statin use because this data was not available. Similarly, the effect of potential confounders, such as over the counter use of non-steroidal anti-inflammatory drugs (NSAIDs) or anticoagulants (e.g. enoxaparin), is also unknown. The IBF is a unique and uncommon endpoint. In a recent study, the 5-year cumulative incidence of prostate cancer mortality for IBF > 18 months versus IBF < 18 months was 9.4% versus 26.3% and corresponding 10-year estimates were 26.2% versus 55.9%, respectively ($p < 0.0001$ for both).(12) While the IBF has been shown to be a negative prognostic factor, it is considered a surrogate of such in this study. Ideally, distant metastasis or prostate cancer mortality would be evaluated as the endpoint. However, the long natural history of prostate cancer and the high degree to which death from other causes in this elderly and aging population competes with prostate cancer death makes such an analysis difficult. It is not known whether men who die due to competing risks are otherwise destined to develop distant metastasis and prostate cancer death because they did not take aspirin or a statin. An IBF < 18 months may be considered “clinically meaningful” BF. An IBF < 18 months detects patients who are at higher risk of clinically meaningful outcomes such as the development of distant metastasis or prostate cancer death.

CONCLUSIONS

In patients who received RT for prostate cancer, aspirin or statin non-use was associated with the early development of BF. While these results are provocative, it is premature to recommend aspirin or statin therapy routinely for men receiving RT for prostate cancer. Aspirin therapy has risks (e.g. peptic ulcers and bleeding) and the optimal dosing schedule is undefined. Statin therapy also has risks, such as rhabdomyolysis, myositis, and liver damage. Further study is needed to confirm these findings and to determine the optimal dosing, schedule, as well as the relative benefits and risks of both therapies in combination with RT.

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Table 1

Various patient and treatment characteristics (n = 2,051).

Characteristic	# (%)
Age (y)	
median	69
range	36 – 86
iPSA level (ng/mL)	
<10	1446 (70)
10 – <20	463 (23)
20	142 (7)
Risk group	
Low	917 (45)
Intermediate	913 (45)
High	219 (11)
T-Stage	
T1	1192 (58)
T2	805 (39)
T3	50 (3)
Gleason score	
2–6	1514 (74)
7	487 (24)
8–10	47 (2)
Radiation dose (Gy)	
Median	76
Range	65 – 82
Treatment fields	
Prostate alone	1000 (49)
Prostate + SVs	467 (23)
Prostate + SVs + LNs	576 (28)
Aspirin use	
No	1,308 (64)
Yes	743 (36)
Aspirin timing	
Initial	158 (21)
Follow-up	288(39)
Both	297(40)
Statin use	
No	1,360 (66)
Yes	691 (34)
Statin timing	
Initial	63 (9)
Follow-up	392 (57)

Characteristic	# (%)
Both	236 (34)

Abbreviations: IMRT = intensity-modulated radiotherapy; 3D-CRT = three-dimensional conformal radiotherapy; iPSA = initial prostate-specific antigen; SVs = seminal vesicles.

Table 2

Aspirin use and interval to biochemical failure (p-value < 0.0001)

Aspirin use	Biochemical failure n (%)		
	IBF 18 months	IBF > 18 months	Total
No	148 (7.2)	1,157 (57)	1,305 (64)
Yes	29 (1.4)	711 (35)	740 (36)
Total	177 (8.7)	1,868 (91)	2045 (100)

Abbreviations: IBF = interval to biochemical failure

Table 3

Statin use and interval to biochemical failure (p-value < 0.0001)

Statin use	Biochemical failure n (%)		
	IBF 18 months	IBF > 18 months	Total
No	154 (7.5)	1,202 (59)	1356 (66)
Yes	23 (1.12)	666 (33)	689 (34)
Total	177 (8.7)	1,868 (91)	2045 (100)

Abbreviations: IBF = interval to biochemical failure

Table 4

Anticoagulant use and interval to biochemical failure (p-value = 0.0006)

Anticoagulant use	Biochemical failure n (%)		
	IBF 18 months	IBF > 18 months	Total
No	168 (8.2)	1,600 (78)	1, 786 (86)
Yes	9 (0.44)	268 (13)	277 (14)
Total	177 (8.7)	1,868 (91)	2045 (100)

Table 5

Cardiovascular disease and interval to biochemical failure (p-value = 0.0008)

Cardiovascular disease	Biochemical failure n (%)		
	IBF 18 months	IBF > 18 months	Total
No	136 (6.7)	1,200 (59)	1,336 (65)
Yes	41 (2.0)	668 (33)	709 (35)
Total	177 (8.7)	1,868 (91)	2045 (100)

Abbreviations: IBF = interval to biochemical failure

Table 6

Odds ratio estimates of IBF < 18 months.

Variable	Odds ratio	95% Confidence Interval	
Aspirin	2.052	1.328	3.172
Anticoagulant	1.932	0.951	3.925
Statin	2.465	1.529	3.974
Initial PSA < 10 ng/dL	1.005	0.991	1.018
Cardiovascular disease	1.255	0.859	1.833

Abbreviations: IBF = interval to biochemical failure