Am J Clin Exp Urol 2018;6(3):123-132
www.ajceu.us /ISSN:2330-1910/AJCEU0074385

Original Article

The impact of celecoxib on outcomes in advanced prostate cancer patients undergoing androgen deprivation therapy

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Received February 10, 2018; Accepted April 23, 2018; Epub June 15, 2018; Published June 25, 2018

Abstract: Recent work suggests the selective Cox-2 inhibitor celecoxib delays progression to androgen independence in hormone sensitive prostate cancer (HSPC) through inhibition of the androgen receptor (AR) and ErbB signaling. However, human studies examining its effect on delaying disease progression while on hormone therapy are limited. This study explores the effect of celecoxib use on PC survival in VA patients undergoing androgen deprivation therapy (ADT) for advanced PC. We retrospectively examined the association between celecoxib use (defined as duration of medication use ≥180 days) in men with PC being treated with ADT in national VA databases. Patients were diagnosed with PC from 2000-2008 and had follow-up through May 2016. Clinical, pathologic and demographic variables were compared by celecoxib use, using Mann-Whitney U test and Chi-squared tests. Associations between celecoxib use and overall survival (OS), skeletal related events (SRE), and cancer specific survival (CSS) were performed using adjusted Cox proportional hazard models. Overall, 87,344 patients with PC on ADT were identified. Patients on celecoxib (n=1,581) had lower PSA levels at both diagnosis (7.0 versus 8.7 ng/mL, P<0.001) and initiation of ADT (6.2 versus 7.3 ng/mL, P=0.002) compared to patients not taking celecoxib (n=85,763). Gleason score (P=0.14), death from PC (P=0.07), and number of SREs (P=0.18) were similar between groups. In the Cox multivariable analysis, celecoxib use was not associated with improved OS (hazard ratio, HR, 1.06, 95% confidence interval, CI, 0.93-1.21, P=0.38), risk of SRE (HR 0.95, 95% CI 0.62-1.44, P=0.80), or improved CSS (HR 1.00, 95% CI 0.78-1.28, P=0.98). Despite an association with lower PSA levels, celecoxib use in PC patients on ADT was not associated with improved cancer outcomes.

Keywords: Advanced prostate cancer, celecoxib, androgen deprivation therapy

Introduction

Despite six new therapies approved by the United States Food and Drug Administration for the treatment of men with advanced prostate cancer (PC) in the last decade [1], in 2017 nearly 27,000 men will die from PC in the United States [2]. Novel therapeutic options for men that fail conventional treatments are imperative. Androgen deprivation therapy (ADT) remains the standard first line approach for metastatic hormone sensitive PC (mHSPC). Although a majority of patients will initially respond to ADT, most will inevitably develop androgen independent or castrate-resistant PC (CRPC) defined as disease progression despite serum testosterone levels of less than 20 ng/dL. Genomic and proteomic alterations involving the androgen receptor (AR) and multiple growth factor pathways permit PC cell proliferation and growth in an androgen depleted environment [3, 4]. The treatment of residual PC cells during initial ADT application represents an underexplored therapeutic niche that may lead to improved outcomes in men with advanced disease. Several recent Phase III trials (GETUG-AFU 15, CHAARTED, and STAMPEDE) have demonstrated that docetaxel chemotherapy and ADT for mHSPC synergistically leads to improvements in overall survival (OS), up to 13.6 months, compared to ADT alone in hormone naïve patients. These data suggest that the initiation of ADT induces susceptibilities in PC cells that make them amenable to synergistic treatments [5-7].

Celecoxib is a cyclooxygenase (Cox)-2 selective nonsteroidal anti-inflammatory medication (NSAID) commonly prescribed to reduce pain and inflammation. There is encouraging basic

and clinical evidence for the chemopreventative and antineoplasic effects of celecoxib [8-12], however human studies examining celecoxib effect on delaying disease progression while on hormone therapy are limited. Recent laboratory work suggests that celecoxib at the time of castration delays progression from androgen dependence to independence in PC cell lines and rodent models [13]. A possible mechanism by which celecoxib delays disease progression is through inhibiting the androgen receptor (AR)-EGFR and ErbB signaling pathway [14]. We conducted a large observational study evaluating the impact of celecoxib use on PC survival in Veterans Affairs (VA) patients being treated with ADT for advanced PC.

Materials and methods

Data source

The study was approved by local Institutional Review Boards (IRB) to query the national Veterans Health Administration (VA) databases for this observational study. The VA provides care to over 20 million Veterans at over 1,400 centers. All care processes are captured via an electronic health record (EHR) known as the Veterans Information System Technology Architecture (VistA) that provides a longitudinal view for patients receiving care nationwide including diagnoses, procedures, medications, labs, physiologic measurements, text notes and reports [15]. Data are aggregated from individual VistA systems to the VA Corporate Data Warehouse (CDW) where it is modeled and prepared for use. Researchers may request access to IRB-approved project-specific data that is then extracted from source databases and placed in tables accessible only to the research team.

Study population

To develop a cohort of men with PC on ADT, we identified all men diagnosed with PC (ICD-9 code 185) in the VA CDW from 2000-2008 (n=558,252). Within this cohort, we narrowed our population to include only those with ADT use (n=129,672) by querying the pharmacy domain for VA formulary approved ADT medications including leuprolide, goserelin, bicalutamide, flutamide, and nilutamide from 2000 through May 31, 2016. We excluded patients with no information for ADT medication supply days/quantity/dose, those taking ADT for ≤180 days (n=33,312), and/or those receiving ADT concurrently with definitive radiation therapy of the prostate (n=10,960) leaving us a final cohort of 87,344 patients for our analytic file. Longitudinal data on each patient was compiled until death or study end of May 31, 2016 at which point they were censored.

We divided the study population into two cohorts and defined celecoxib use within the VA as having a prescription for celecoxib for ≥180 days during the study period. The comparator group included no prescription of celecoxib for ≥180 days during study period.

Outcomes of interest

The primary outcome of interest in this study is overall survival (OS). Secondary outcomes of interest for this study include skeletal related events (SRE) and death from PC (CSS). The dependent variable used in our analyses is the time interval between the starting date of ADT to death from any cause, SRE, and/or death from PC observed during the study period. SRE was used as a surrogate for progression and we used a previously described claims-based model to identify SRE from indicators including pathologic fracture, spinal cord compression, and/or radiation and bone surgery [16].

Predictors and measures

The celecoxib group consisted of patients who had celecoxib of any dose prescribed for ≥180 days. We did not exclude patients that also had exposures to other NSAID medications. Prior clinical trials on celecoxib consisted of at least 90 days' exposure; therefore, we chose to define medication use of at least 180 days based on these studies [17, 18]. Non-celecoxib users were patients that had no prescription for celecoxib for ≥180 days.

Covariates adjusted for in the analyses included demographic and clinical characteristics of each patient. Demographic and clinical covariates collected included age at ADT initiation, race, Charlson Comorbidity score (CCI), Agent Orange exposure, year of diagnosis, statin use, prostate specific antigen (PSA) at diagnosis, Gleason score, and docetaxel use.

Statistical analysis

Statistical analysis was performed using Stata 14 (College Station, TX). The Mann-Whitney U

Table 1. Cohort breakdown

	Non-celecoxib (N=85,763)	Celecoxib (N=1,581)	*P*-value
Age, median (IQR)	75 (68-79)	75 (70-79)	0.003
Race, n (%)			
White	54,253 (63.3)	1,064 (67.3)	<0.001
Black	16,480 (19.2)	355 (22.5)	
Other	15,030 (17.5)	162 (10.3)	
Charlson Comorbidity score, n (%)			
0-1	66,243 (77.2)	1,272 (80.5)	0.009
2-3	17,083 (19.9)	267 (16.9)	
> 3	2,437 (2.8)	42 (2.7)	
Agent Orange exposure, n (%)	3,423 (4.0)	52 (3.3)	0.16
Prostate specific antigen (PSA)*, median (IQR)	8.7 (2.3-20.2)	7.0 (1.9-15.9)	<0.001
Prostate specific antigen (PSA)*, n (%)			
<4	14,546 (17.0)	303 (19.2)	0.002
4-10	12,217 (14.3)	258 (16.3)	
>10	21,918 (25.6)	361 (22.8)	
Missing	37,082 (43.2)	659 (41.7)	
Prostate specific antigen (PSA**, median (IQR)	7.3 (1.3-20.5)	6.2 (1.2-16.1)	0.002
Prostate specific antigen (PSA)**, n (%)			
<4	23,643 (27.6)	471 (29.8)	0.002
4-10	13,234 (15.4)	283 (17.9)	
>10	26,498 (30.9)	444 (28.1)	
Missing	22,388 (26.1)	383 (24.2)	
Gleason score, n (%)			
6	6,216 (7.3)	111 (7.0)	0.14
7	7,758 (9.1)	133 (8.4)	
8-10	10,045 (11.7)	160 (10.1)	
Missing	61,744 (71.9)	1,177 (74.5)	
Vital status, n (% deceased)	65,571 (76.5)	1,289 (81.5)	<0.001
Overall survival, years median (IQR)	5.4 (2.7-9.1)	5.8 (3.0-9.4)	<0.001
Death from prostate cancer, n (%)	8,637 (10.1)	181 (11.5)	0.07
Skeletal related event, n (%)	8,139 (9.5)	166 (10.5)	0.18
Time to skeletal related event, years median (IQR)	4.9 (2.3-8.5)	5.3 (2.7-8.9)	0.003

*PSA at diagnosis (ng/dl), **PSA at initiation of ADT (ng/dl).

Table 2. Cohort medication history

	Non-celecoxib N=85,763	Celecoxib N=1,581	*P*-value
Docetaxel, n (%)	2,858 (3.3)	37 (2.3)	0.03
Statin, n (%)	52,332 (61.0)	1,026 (64.9)	0.002
Finasteride, n (%)	14,812 (17.3)	377 (23.9)	<0.001
Aspirin, n (%)	44,858 (52.3)	975 (61.7)	<0.001

test was used for comparison of continuous variables and Chi-squared test was used for comparison of categorical variables. We assessed the association of baseline demographic and clinical characteristics stratified by groups as noted above. We performed multivariable Cox proportional hazards analyses to assess for independent predictors of OS, SRE, and CSS. We constructed Kaplan-Meier curves for OS, SRE, and CSS and performed log rank tests. A two-sided *P*-value of <0.05 was considered significant.

Results

The total cohort available for analysis after exclusion consisted of 87,344 patients. Of these PC patients on ADT, 1,581 (2%) were on

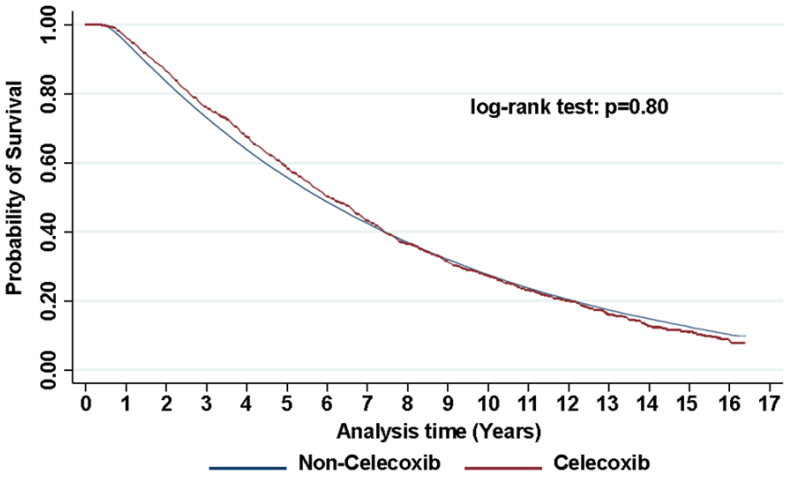

Figure 1. Kaplan-Meier curve for overall survival stratified by celecoxib use (Log rank test).

Table 3. Cox proportional hazards multivariable analysis assessing predictors of overall survival

	Hazards Ratio	95% CI	*P*-value
Celecoxib usage			
No	Referent	Referent	
Yes	1.06	0.93-1.21	0.38
Age (continuous)	1.04	1.04-1.04	<0.001
Race			
White	Referent	Referent	
Black	0.90	0.86-0.94	<0.001
Other	0.94	0.89-0.99	0.03
Charlson-comorbidity score			
0-1	Referent	Referent	
2-3	1.16	1.11-1.21	<0.001
>3	1.90	1.75-2.06	<0.001
Agent Orange exposure			
No	Referent	Referent	
Yes	0.93	0.85-1.02	0.12
Year of diagnosis			
2000-2004	Referent	Referent	
2005-2008	0.95	0.92-0.99	0.01
Statin usage			
No	Referent	Referent	
Yes	0.64	0.62-0.66	<0.001
Prostate specific antigen (category)*			
<4	Referent	Referent	
4-10	0.96	0.90-1.02	0.16
>10	1.13	1.07-1.19	<0.001
Gleason score			
6	Referent	Referent	
7	1.09	1.03-1.14	0.001
8-10	1.44	1.37-1.51	<0.001
Docetaxel Usage	1.98	1.85-2.12	<0.001

*PSA at diagnosis.

celecoxib and 85,763 (98%) were not. Clinicopathologic characteristics of the population analyzed are listed in **Table 1**. There were more African-Americans taking celecoxib (22.5%) compared to the non-celecoxib (19.2%, P< 0.001) group. The celecoxib group had slightly lower Charlson Comorbitiy Indices (80.5% CCI 0-1) compared to non-celecoxib (77.2% CCI 0-1, P=0.009). The celecoxib group also had lower PSAs at both diagnosis (7.0 versus 8.7 ng/mL, P<0.001) and initiation of ADT (6.2 versus 7.3 ng/mL, P=0.002) compared to no celecoxib. Agent Orange exposure (P=0.16) and Gleason scores (P= 0.14) were similar between groups. The celecoxib group was more likely to be taking statin (P=0.002), finasteride (P<0.001), and aspirin (P<0.001) medications (**Table 2**).

The proportion of deceased patients was higher in the celecoxib group (81.5%) compared to the non-celecoxib (76.5%, P<0.001) group. The median OS was 5.8 (IQR 3.0-9.4) in the celecoxib group and 5.4 years (2.7-9.1) in the non-celecoxib group as represented in the Kaplan Meier curve (**Figure 1**, P=0.80). The Cox proportional hazards multivariable analysis adjusting for age, race, CCI, Agent Orange exposure, year of diagnosis, statin use, PSA, Gleason score, and docetaxel use revealed that the celecoxib group (non-celecoxib referent group) was not associated with improved OS (hazard ratio, HR,

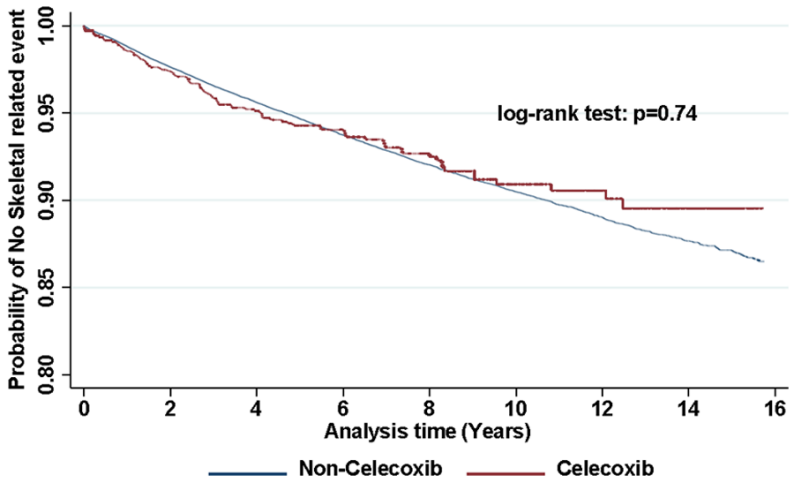

Figure 2. Kaplan-Meier curve for skeletal related events stratified by celecoxib use (Log rank test).

Table 4. Cox proportional hazards multivariable analysis assessing predictors of skeletal related events

	Hazards Ratio	95% CI	*P*-value
Celecoxib usage			
No	Referent	Referent	
Yes	0.95	0.62-1.44	0.80
Age (continuous)	0.98	0.97-0.98	<0.001
Race			
White	Referent	Referent	
Black	1.00	0.89-1.12	0.99
Other	0.84	0.72-0.99	0.03
Charlson-comorbidity score			
0-1	Referent	Referent	
2-3	1.14	1.01-1.29	0.03
>3	1.48	1.16-1.89	0.002
Agent Orange exposure			
No	Referent	Referent	
Yes	1.02	0.85-1.23	0.80
Year of diagnosis			
2000-2004	Referent	Referent	
2005-2008	1.23	1.11-1.36	<0.001
Statin usage			
No	Referent	Referent	
Yes	0.63	0.57-0.70	<0.001
Prostate specific antigen (category)*			
<4	Referent	Referent	
4-10	0.88	0.74-1,03	0.12
>10	0.95	0.82-1.11	0.53
Gleason score			
6	Referent	Referent	
7	1.02	0.89-1.18	0.76
8-10	1.46	1.28-1.66	<0.001
Docetaxel Usage	2.63	2.27-3.06	<0.001

*PSA at diagnosis.

1.06, 95% confidence interval, CI, 0.93-1.21, P=0.38) (**Table 3**).

The proportion of patients with SRE was similar between the celecoxib (10.5%) and non-celecoxib groups (9.5%, P=0.18). The median time to SRE was 5.3 years (IQR 2.7-8.9) in the celecoxib group and 4.9 (2.3-8.5) in the non-celecoxib group as represented in the Kaplan Meier curve (**Figure 2**, P=0.74). The Cox proportional hazards multivariable analysis showed no decreased risk of SRE (HR 0.95, 95% CI 0.62-1.44, P=0.80) with celecoxib use (**Table 4**). During the study period, 11.5% in the celecoxib group and 10.1% in the non-celecoxib group died as represented in the Kaplan Meier curve (**Figure 3**, P=0.38). The Cox proportional hazards multivariable analysis was not associated with improved CSS (HR 1.00, 95% CI 0.78-1.28, P=0.98) (**Table 5**) in men taking celecoxib.

Discussion

This large observational cohort study identifies that celecoxib use is not independently associated with improved oncologic outcomes in men with HSPC also taking ADT. Prior clinical trials evaluating the impact of celecoxib on men with PC have provided mixed results. The current study is unique in evaluating the impact of celecoxib use on OS, SRE, and CSS in men with advanced HSPC on ADT in a large cohort. Capture of outpatient medication use is of vital importance for this type of analy-

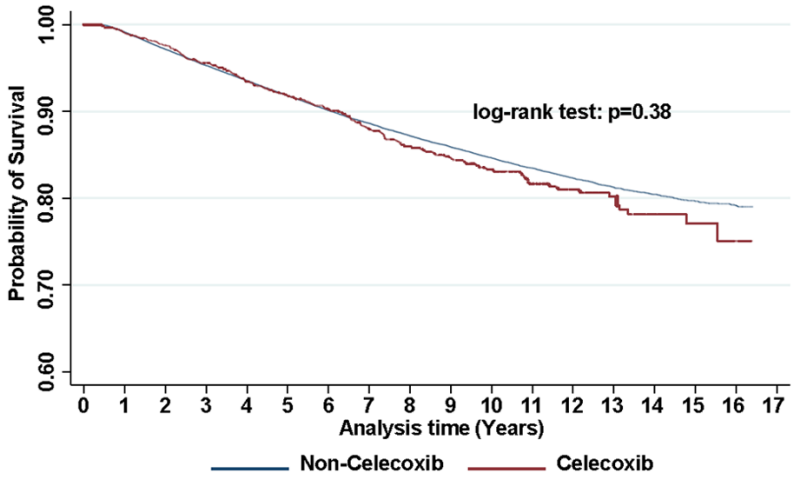

Figure 3. Kaplan-Meier curve for prostate cancer specific mortality stratified by celecoxib use (Log rank test).

Table 5. Cox proportional hazards multivariable analysis assessing predictors of prostate cancer-specific survival

	Hazards Ratio	95% CI	*P*-value
Celecoxib usage			
No	Referent	Referent	
Yes	1.00	0.78-1.28	0.98
Age (continuous)	1.02	1.02-1.03	<0.001
Race			
White	Referent	Referent	
Black	1.00	0.93-1.07	0.95
Other	0.95	0.86-1.05	0.30
Charlson-comorbidity score			
0-1	Referent	Referent	
2-3	1.14	1.06-1.24	0.001
>3	1.65	1.42-1.92	<0.001
Agent Orange exposure			
No	Referent	Referent	
Yes	0.88	0.76-1.02	0.09
Year of diagnosis			
2000-2004	Referent	Referent	
2005-2008	0.89	0.83-0.95	<0.001
Statin usage			
No	Referent	Referent	
Yes	0.53	0.50-0.57	<0.001
Prostate specific antigen (category)*			
<4	Referent	Referent	
4-10	0.86	0.77-0.96	0.006
>10	1.14	1.04-1.26	0.006
Gleason score			
6	Referent	Referent	
7	1.13	1.03-1.24	0.01
8-10	1.99	1.82-2.17	<0.001
Docetaxel Usage	2.93	2.66-3.24	<0.001

*PSA at diagnosis.

sis. VA databases provide an ideal platform for performing this study with over 80% of VA enrollees who use their VA pharmacy benefits filling their prescriptions through the VA pharmacy [19]. Additionally, the VA provides continuous care for the majority of these Veterans, monitored through one healthcare record, making outcomes easier to assess.

Celecoxib is the only United States Food and Drug Administration approved selective Cox-2 NSAID currently available. These selective Cox-2 inhibitors were designed to provide the anti-inflammatory effects of non-selective NSAIDS with a reduced risk of gastrointestinal side effects. However, their use has been tempered by an increased cardiovascular risk [20, 21]. Case control trials of Cox-2 inhibitors prescribed for the treatment of arthritis between 1999 and 2005 demonstrated an overall 68% risk reduction for multiple cancers, including PC. Specifically, a meta-analysis of 17 independent studies demonstrated a 27% reduction in the relative risk (RR) of PC (combined RR 0.73, 95% CI 0.62-0.87) [22]. In light of the potential chemopreventative effects and increased cardiovascular risk, a meta-analysis of 72 studies showed no evidence that celecoxib increased the relative risk of cardiovascular disease [23]. In contrast, the Adenoma Prevention with Celecoxib Trial examining the safety and efficacy of

celecoxib for colorectal adenoma prevention in high risk patients showed an increased risk of cardiovascular and thrombotic events in patients with a baseline history of atherosclerotic heart disease [24]. Recently, celecoxib has been shown to be non-inferior compared to both ibuprofen and naproxen with regards to cardiovascular safety [25]. In sum, cardiovascular events do not appear to be markedly increased with use of celecoxib in patients without pre-existing atherosclerotic heart disease.

Our study aimed to specifically assess the effects of celecoxib use on those patients also taking ADT based on the potential for synergy between these agents. ADT leads to disease regression, however through clonal selection cells with multiple genomic and proteomic alterations, a majority through AR and alternative growth factor pathways, persist. The culmination of these alterations involves the ability of PC cells to grow and proliferate in an androgen-depleted environment [3, 4]. Laboratory models suggest celecoxib delays progression to androgen independent PC. Celecoxib inhibited growth and activation of multiple cell survival makers, including Akt, Erk1/2, and NF-κB, in LNCaP cells and showed strong inhibitory effect on the progression of androgen-dependent to independent LNCaP tumors in castrated SCID mice [13]. Recent evidence suggests celecoxib delays progression to androgen independence through inhibiting AR-EGFR signaling pathway and Cox-2-ErbB family receptor network interaction. Celecoxib reduces ErbB family member protein expression, including ErbB3 strongly implicated in castration-resistant PC, through lysosome activation and Nrdp 1 induction and AR expression through hnRNP K downregulation [14].

In advanced HSPC, an analysis of the STAMPEDE multi-arm, multistage, randomized controlled trial examined hormone therapy plus celecoxib compared to hormone therapy alone in 2043 patients with newly diagnosed or with rapidly relapsing PC and hormone naïve. Results showed no improvement in OS with hormone therapy plus celecoxib compared to hormone therapy alone (HR 0.94, 95% CI 0.74-1.20). Celecoxib was discontinued early due to lack of benefit [26]. Additionally, no improvement in all-cause mortality was seen when celecoxib with or without zoledronic acid was combined with standard of care (continuous hormone therapy for metastatic disease or for ≥2 years for non-metastatic disease) in 1,245 hormone naïve patients (celecoxib HR 0.98, 95% CI 0.80-1.20, P=0.85; celecoxib + zoledronic acid HR 0.86, 95% CI 0.70-1.05, P=0.13) [27]. These results suggest that celecoxib may not provide additional survival benefit in hormone-naïve patients.

In the current study, the largest analysis to date, we found no improvement in OS in the celecoxib group compared to the non-celecoxib group in our adjusted Cox proportional hazards multivariable analysis. We adjusted for multiple covariates, including age at ADT initiation, race, CCI, Agent Orange exposure, year of diagnosis, statin use, PSA at diagnosis, Gleason score, and docetaxel use. Our results also showed no improvement in risk of SRE, which we used as a marker of disease progression, or CSS. Other medications, most notably statins, may interact with celecoxib, as may the duration of use of these medications. *In vitro* and *in vivo* models have demonstrated celecoxib and statins have a synergistic effect on delaying PC progression [13]. Previous studies examined the effects of celecoxib after a minimum of 90 days, supporting our criteria of ≥180 days' celecoxib use to be included in the celecoxib group.

The celecoxib group had significantly lower PSA at both diagnosis and at initiation of ADT compared to the non-celecoxib group. The mechanism by which Cox-2 inhibitors potentially reduce PSA is underexplored. However, the cyclooxygenase 2 (Cox-2) is an inducible enzyme isoform that converts arachidonic acid to multiple pro-inflammatory prostaglandins. The association between inflammation and elevated PSA has been clearly established [28]. Therefore, the results of our study could be a result of reduced intraprostatic inflammation in the celecoxib group compared to the non-celecoxib group; however, clinical trials failed to demonstrate a reduction in multiple biomarkers, including prostaglandins, in prostatectomy tissue of patients treated with celecoxib [29-31]. The link between AR activation, either ligand-dependent, as in HSPC, or ligand-independent, as in castrate resistant disease, and PSA expression is also well established [32]. However, previously mentioned clinical trials showed no change in AR activity with celecoxib compared to placebo [29]. Clearly, this is an area of future investigation.

There are several limitations of this study. As a retrospective non-randomized observational study there is the potential for unmeasured confounding and/or missing variables. However, large observational studies like this help identify associations and generate data driven hypotheses. Additionally, as the national VA data is developed as an administrative dataset via the CDW, we cannot account for reasons for medication discontinuation, complete and consistent laboratory data for the entire cohort, body mass index, exercise, smoking status, and PC stage. However, our large sample size allows us to control for other potential important confounders including CCI, Gleason score, and PSA. Finally, our population of aging United States Veterans on ADT may lack external validity.

In the largest observational study to date, despite being associated with lower PSA levels, celecoxib use in PC patients on ADT was not associated with improved OS, risk of SRE, or CSS. This suggests no benefit to Cox-2 inhibitors in HSPC.

Acknowledgements

This material is the result of work supported with resources and the use of facilities at the William S. Memorial Veterans Hospital. The contents do not represent the views of the U. S. Department of Veterans Affairs or the United States Government. This work was supported by a Department of Defense Prostate Cancer Research Program (PC150221). The authors would like to acknowledge and thank all of the women and men that have served their country in the Unites States Armed Forces.

Disclosure of conflict of interest

None.

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