Published in final edited form as:

BJU Int. 2018 February ; 121(2): 244–251. doi:10.1111/bju.14009.

Effects of Thiazolidinedione in Patients with Active Bladder Cancer

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Abstract

OBJECTIVE—To examine the influence of perioperative thiazolidinedione (TZD) on cancer-specific outcomes in patients undergoing radical cystectomy (RC) for urothelial carcinoma (UC).

DESIGN, SETTING, AND PARTICIPANTS—A retrospective cohort of 173 diabetic patients undergoing RC from 2005 to 2010 was identified. Of those, 53 were on TZD treatment at the time of surgery, with 33 patients taking pioglitazone. Baseline clinicopathologic characteristics, as well as cancer specific survival (CSS), recurrence free survival (RFS), and overall survival (OS) were compared between the patients on and off of TZD at the time of RC. In subgroup analysis, outcomes in patients specifically taking pioglitazone at the time of surgery were compared to those not on TZD.

RESULTS—Baseline clinicopathologic characteristics were similar between patients on and off of TZD treatment at the time of RC. Overall, the median CSS rate was not reached in either group ($p=0.7$). The estimated 5-year CSS was 67.8% in the non-TZD group and 66.3% in the TZD group. On multivariate analysis incorporating patient age, pathologic T staging, and adjuvant chemotherapy, TZD use was found not to be a significant predictor for CSS (HR 1.20; 95% CI, 0.66–2.17, $p=0.5$). Additionally, recurrence free survival (RFS) ($p=0.3$) and OS ($p=0.2$) were also similar between the two groups without adjusting for other variables. Comparison between patients taking pioglitazone vs. patients not taking TZD yielded similar CSS ($p=0.2$), RFS ($p=0.5$), and OS ($p=0.2$).

CONCLUSIONS—CSS, as well as RFS and OS after RC were not compromised in patients on TZD therapy at the time of RC. Additional investigation is warranted in non-muscle invasive

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Conflict of interest: None

bladder cancer (NMIBC) and muscle invasive bladder cancer (MIBC) patients undergoing bladder sparing procedures to assess the safety of using TZD in the setting of active UC.

Keywords

Thiazolidinedione; PPAR γ agonist; bladder cancer; BCG

INTRODUCTION

Much debate has surrounded the link between thiazolidinedione (TZD) use and urothelial cancer (UC) of the bladder. First demonstrated in animal studies, urothelial carcinogenesis observed after TZD treatment was attributed to crystallization of calcium- and magnesium-containing uroliths and the associated alterations in urine composition (1). In line with these findings, rosiglitazone was also described to enhance hydroxybutyl(butyl)nitrosamine induced urothelial carcinogenesis (2). Subsequent data from the PROspective pioglitazone Clinical Trial in macrovascular Events (PROactive) as well as the interim analysis of an observational cohort study conducted in the Kaiser Permanente of Northern California (KPNC) database seemed to implicate a similar association between the incidence of UC with prolonged pioglitazone intake in humans (3, 4).

As a result, The United States Food and Drug Administration (FDA) issued a public safety announcement in 2011 regarding the increased risk of UC after more than 1 year of treatment with pioglitazone. Conjointly, recommendations were made against the use of pioglitazone in patients with active UC. Soon after, the European Medicines Agency (EMA) followed suit, also issuing warnings regarding a slightly increased risk of UC with pioglitazone and prohibiting its use in patients with history of bladder cancer or uninvestigated hematuria.

Since then, emerging evidence from the long-term observational data of the PROactive clinical trial, as well as the final report of the KPNC cohort study, suggested that the increased risk of UC with pioglitazone use observed early on had resolved with long-term follow-up (5, 6). Moreover, no data regarding the clinical effects of TZD in patients with active UC exists in the current literature. To this end, we aimed to examine the role of TZD at the time of radical cystectomy (RC) in patients diagnosed with UC. On the basis of the limited specificity of TZD-associated tumorigenesis in rats, we hypothesized that perioperative TZD use does not affect cancer specific outcomes.

PATIENTS AND METHODS

After institutional review board approval, we retrospectively searched for patients undergoing RC at University of Texas, M.D. Anderson Cancer Center prior to the revisions of the FDA labeling for pioglitazone concerning its potential risk for bladder cancer. Between January 2005 and December 2010, 862 patients were identified. Of those, 173 were diagnosed with diabetes mellitus. Overall, 53 patients were on TZD treatment at the time of surgery. Of the patients on TZD, 20 were treated with rosiglitazone, while 33 were treated with pioglitazone.

Collected clinicopathologic characteristics included age, gender, body mass index (BMI), smoking history, diabetes mellitus status, American Society of Anesthesiologists scores, clinical and pathologic tumor staging according to the 7th AJCC Cancer Staging manual, receipt of intravesical immunotherapy with BCG, neoadjuvant, and adjuvant systemic chemotherapy. All histologic specimens were reviewed at M.D. Anderson Cancer Center by subspecialty genitourinary pathologists. Recurrent cancers post-RC were detected on imaging with or without histologic evidence, and were correlated with the post-RC clinical course. Deaths were designated as cancer-specific when patients succumbed to disease within 12 months of metastasis or due to perioperative complications within 90 days of cystectomy. Survival was calculated from the date of RC.

The primary comparison was between the CSS in patients on and off of TZD treatment at the time of RC. Multivariate Cox proportional hazards model was performed to evaluate whether perioperative TZD intake independently predicted for CSS. In addition, the RFS and OS of the two groups were analyzed. As the FDA warning was limited to pioglitazone, subgroup analysis was performed comparing the RFS, CSS, and OS of patients specifically taking pioglitazone vs. those not on TZD at the time of RC.

Statistical analysis was performed using STATA/SE version 14.1 statistical software (Stata Corp. LP, College Station, TX). Continuous variables were summarized using the mean and standard deviation (SD), and categorical variables using frequency count and percentage. Two-sample Wilcoxon rank-sum test and Pearson's chi-squared tests were used for comparison of continuous and categorical variables, respectively. CSS, RFS and OS were estimated using the Kaplan-Meier methods and compared using the log-rank test. Multivariate analysis was performed using the Cox regression model. All tests were two-sided and $p < 0.05$ was considered statistically significant.

RESULTS

Of the 173 patients with DM undergoing RC, 53 were on TZD treatment at the time of surgery. Baseline demographics are shown in Table 1. Notably, BMI in the TZD group was higher (33.2 vs. 30.3 kg/m², $p = 0.006$), possibly reflective of their higher severity of metabolic syndrome. In addition, slightly more patients in the non-TZD group had smoking history (95.8 vs. 86.8%, $p = 0.03$). Clinical staging was similar between the two groups. In the non-TZD group, 45.8%, 41.7% and 12.5% were staged <cT2, cT2 and >cT2, respectively. The corresponding percentages in the TZD group were 47.2%, 41.5% and 11.3% ($p = 0.9$). The proportions within each group having undergone intravesical BCG and neoadjuvant chemotherapy were similar (Table 1).

In the non-TZD group, 51.6%, 17.5% and 30.8% had pathologic staging <pT2, pT2 and >pT2, respectively. The corresponding percentages in the TZD group were 54.7%, 7.5%, and 37.7% ($p = 0.5$). In addition, similar proportions of patients had pathologic node positive (non-TZD 18.4%, TZD 22.6%, $p = 0.3$) and metastatic disease (non-TZD 5%, TZD 0%, $p = 0.2$). Similar rates of patients received adjuvant chemotherapy in each group.

Mean followup after cystectomy were 49.3 mo (Range 0.5–115 mo) for the non-TZD group and 48.1 mo (Range 0.4–130.7 mo) for TZD group ($p=0.7$). Overall, 35 (29.2%) and 17 (32%) deaths due to UC occurred during the followup period in the non-TZD and TZD groups, respectively. For both the non-TZD and TZD groups, median CSS were not reached ($p=0.7$) (Fig. 1a). Estimated 5-year CSS were 67.8% (95% CI, 57.9–75.9%) in the non-TZD group vs. 66.3% (50.7–78.0%) in the TZD group. On multivariate analysis incorporating age, pT staging, and adjuvant chemotherapy, TZD use was found not to be a significant predictor for CSS (HR 1.20; 95% CI, 0.66–2.17, $p=0.5$) (Table 2b). Furthermore, no difference was found in the RFS (median RFS non-TZD: 31 mo, 95% CI 16–57 mo vs. TZD: 45 mo, 95% CI 24–72 mo, $p=0.3$) and OS (median OS non-TZD: 73 mo 95% CI 42–99 mo vs. TZD: 49 mo, 95% CI 26–70, $p=0.2$) in the two groups (Fig. 1).

A total of 33 patients were specifically on pioglitazone treatment at the time of RC. Similar to the TZD group overall, patients taking pioglitazone at the time of RC had higher BMI and lower incidence of smoking history than the non-TZD group (Table 1). Median RFS, CSS and OS for the patients taking pioglitazone were 37 mo (95% CI, 14–88 mo), 71 mo 24–NR mo), and 46 mo (23–90 mo), respectively (Fig. 3). No difference was found in RFS, CSS, or OS between patients on pioglitazone and no TZD at the time of RC.

DISCUSSION

To our knowledge, the current study is the first to evaluate the clinical effects of oral TZD on patients with active UC. No detriment was observed in regards to the CSS, RFS, or OS in patients taking TZD at the time of RC. As the FDA and EMA have recently reiterated their warnings against the use of pioglitazone in patients with active UC (7), no prospective study is possible to test the validity of the concern for cancer exacerbation. Barring future changes by these agencies, our study serves as a unique comparison of the clinical outcomes of UC patients with and without perioperative use of TZD.

Previously, one small study reported a similar pathologic staging distribution between diabetic patients undergoing RC with ($n=9$) and without ($n=24$) pioglitazone treatment (8). Similarly, no difference was observed between the TZD and non-TZD groups in the current study. However, our cohort composed of significantly higher proportion of patients with non-muscle invasive bladder cancer (51.6% vs. 24.1% in non-TZD patients and 54.7% vs. 22.2% in TZD patients). This discrepancy can either be due to difference in practice patterns or a statistical artifact of the small sample size in the previous study.

The lack of difference in oncologic outcomes due to TZD treatment corroborates with long term follow-up data from the PROactive trial and the KPNC longitudinal cohort study, showing no difference in the incidence of bladder cancer between TZD users and controls (5, 6). It has been suggested that the resolution of the statistical difference on the long-term follow-up may be due to a time-dependent manner in which bladder cancer was induced by pioglitazone. However, this theory was disproven in a separate analysis of the KPNC study, in which similar results were found when patients were censored at 1 year after discontinuation of pioglitazone (6). These results were corroborated by other prospective and retrospective studies in diverse populations (9, 10). A systematic review of this topic

demonstrated discrepant results, with some studies finding no association, some a modest association, while others more pronounced associations (11).

On the other hand, evidence for increased bladder carcinogenesis with TZD intake has been modest at best. The only study to date implicating TZD as a promoter of carcinogenesis in the setting of active UC was conducted in Fischer-344 female rats using the hydroxybutyl(butyl)nitrosamine induced tumor model (2). Rosiglitazone, even when administered relatively late in the carcinogenic process, led to decreased cancer latency and a large increase in cancer incidence. The tumorigenic effect was thought to be due to signaling via the peroxisome proliferator-activated receptor gamma (PPAR γ) pathway, a transcription factor involved in the regulation of glucose and lipid homeostasis, inflammation, proliferation, and differentiation (12). The exact role of PPAR γ activation in carcinogenesis remains uncertain and seems disparate in different tumor types (12). Germane to bladder cancer, PPAR γ is thought to be intimately involved in the regulation of VEGF, leading to increased angiogenesis and tumor growth (13). On the other hand, PPAR γ agonists have also been repeatedly demonstrated to decrease UC viability (14) and to inhibit cellular proliferation (15) and tumor growth (16). Regardless of its mechanism of action, the tumor enhancing ability of TZD has not been replicated in other animal studies or with data from human trials.

The evidence for the induction of UC by pioglitazone is equally dubious. Notwithstanding its statistical significance, the PROactive trial found an increase of only eight cases in a total of 2605 patients on pioglitazone therapy, translating to a difference of 0.3% compared to control (3). The KPNC data supporting enhanced tumorigenesis were equally suspect. The 5-year interim analysis revealed only a weak signal of increased UC incidence in prolonged pioglitazone users (OR 1.4; 95% CI, 1.03–2.10) and no such increase in the overall cohort (4). Despite the emerging favorable long-term evidence (5, 6), the FDA recently chose to retain its warning that pioglitazone use is possibly associated with a higher risk of UC (7).

The results from the current study lead to the provocative conjecture that notwithstanding its dubious link to the induction of UC, TZD can be safely used in the setting of active UC. This hypothesis, however, needs further validation in larger MIBC sample groups. As RC theoretically removes the greatest proportion of tumor burden, it is vital to also assess cancer specific outcomes in patients on and off of TZD while undergoing other forms of bladder-sparing treatments, such as radical trimodality therapy, systemic chemotherapy, and immunotherapy. Furthermore, the outcomes in NMIBC patients warrant detailed examination, specifically scrutinizing TZDs' influence on outcomes following intravesical therapy, rates of recurrence, and progression to MIBC. However, prospective studies to answer these questions are currently prohibited by the existing warnings from the FDA and EMA. Efforts are underway at our institution to retrospectively evaluate the effect of TZD in these populations.

The current study was not without limitations. Due to the retrospective nature of the review, the duration of TZD intake was not standardized prior to or after RC. As such, it is conceivable that patients may have discontinued therapy upon the FDA Drug Safety Communication issued in August 2011, leading to a dilution of the treatment effect over

time. To combat this problem, we restricted our retrospective query to the end of 2010 in attempt to limit the number of patients terminating TZD therapy shortly after RC. Furthermore, duration of TZD use prior to and after RC could not be universally obtained in the current retrospective cohort. Thus, time dependent effects of TZD use on active UC may not have been evident in the analysis. With the FDA/EMA label warnings still in place, an effective prospective study in the clinical setting of active UC is impossible.

CONCLUSIONS

We present the first analysis of the clinical effects of oral TZD intake on patients with active UC undergoing RC. Post-cystectomy CSS, RFS, or OS were not compromised in patients on TZD therapy or specifically taking pioglitazone at the time of RC.

Acknowledgments

Sources of support: Ann Sutton assisted in the editing of the manuscript. This work was supported in part by the Cancer Center Support Grant (NCI Grant P30 CA016672) and the Bladder SPORE grant.

Abbreviations

FDA	Food and Drug Administration
TZD	Thiazolidinedione
UC	Urothelial cancer
PPARγ	Peroxisome proliferator-activated receptor gamma
RC	Radical cystectomy
RFS	Recurrence-free survival
CSS	Cancer-specific survival
OS	Overall survival
KPNC	Kaiser Permanente Northern California
EMA	European Medicines Agency
BMI	Body mass index
NMIBC	Non-muscle invasive bladder cancer
MIBC	Muscle invasive bladder cancer
BCG	Bacillus Calmette-Guerin

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Overall survival

Figure 1.
Survival in non-TZD and TZD patients. A) Cancer specific survival; b) recurrence free survival; c) overall survival.

Figure 2. Survival in non-TZD and patients on pioglitazone treatment. A) Cancer specific survival; b) recurrence free survival; c) overall survival.

Table 1

Clinicopathologic characteristics

	Thiazolidinedione		Pioglitazone (n=33)	p-value (TZD vs. no TZD)	p-value (pioglitazone vs. no TZD)	
	No (n=120)	Yes (n=53)				
Mean age, years (SD)	69.9 (8.8)	70.5 (7.1)	70.2 (8)	0.685	0.901	
Mean BMI (SD)	30.3 (6.3)	33.2 (8)	34.5 (6.9)	0.006	0.001	
Mean follow-up, months (SD)	49.3 (32.9)	48.1 (35.3)	42.8 (38.9)	0.734	0.291	
Sex, n (%)				0.431	0.466	
Male	101	84.2	42	79.2	26	78.8
Female	19	15.8	11	20.8	7	21.2
Smoker, n (%)				0.031	0.006	
No	5	4.2	7	13.2	6	18.2
Yes	115	95.8	46	86.8	27	81.8
ASA score, n (%)				0.999	0.739	
2	2	1.7	0	0	0	0
3	101	87.8	46	90.2	29	90.6
4	12	10.4	5	9.8	3	9.4
Intravesical BCG, n (%)				0.301	0.333	
No	80	66.7	31	58.5	19	57.6
Yes	40	33.3	22	41.5	14	42.4
BCG unresponsive [*] , n (%)				0.965	0.906	
No	54	76.1	28	75.7	17	77.3
Yes	17	23.9	9	24.3	5	22.7
Neoadjuvant chemotherapy, n (%)				0.756	0.277	
No	74	61.7	34	64.2	22	66.7
Yes	46	38.3	19	35.8	11	33.3
cT stage [§] , n (%)				0.906	0.447	
CIS, cT1a, and cT1	55	45.8	25	47.2	16	48.5
cT2	50	41.7	22	41.5	14	42.4
cT3	8	6.7	2	3.8	0	0
cT4	7	5.8	4	7.5	3	9.1

	Thiazolidinedione			Pioglitazone (n=33)	p-value (TZD vs. no TZD)	p-value (pioglitazone vs. no TZD)
	No (n=120)	Yes (n=53)				
cN stage, n (%)						
N0	120	100 53	100 33	100		
cM stage						
M0	120	100 52	98.1 32	97	0.306	0.056
Mx	0	0 1	1.9 1	3		
pT stage [§]					0.512	0.593
pT0	22	18.3 10	18.9 6	18.2		
CIS pT0 and pT1	40	33.3 19	35.8 13	39.4		
pT2	21	17.5 4	7.5 2	6.1		
pT3	27	22.5 15	28.3 9	27.3		
pT4	10	8.3 5	9.4 3	9.1		
pN stage, n (%)					0.303	0.251
N0	97	80.8 40	75.5 23	69.7		
N1	8	6.7 5	9.4 4	12.1		
N2	9	7.5 7	13.2 5	15.2		
N3	5	4.2 0	0 0	0		
Nx	1	0.8 1	1.9 1	3		
pM stage, n (%)					0.179	0.365
M0	113	95 53	100 33	100		
M1	6	5 0	0 0	0		
Adjuvant chemotherapy, n (%)					0.212	0.525
No	100	83.3 48	90.6 29	87.9		
Yes	20	16.7 5	9.4 4	12.1		

ASA=American Society of Anesthesiologists classification; BCG=Bacillus Calmette-Guerin

* BCG unresponsiveness was defined as high-grade tumor recurrence within 6–9 months of the last exposure to BCG despite adequate BCG treatment (at least five of six induction instillations and two of three maintenance doses of BCG) (17).

[§] Clinical and pathologic tumor staging classified according to the 7th American Joint Committee Cancer Staging Manual.

Statistically significant values denoted in bold.

Table 2

a. Univariate analysis for cancer-specific survival			
	HR	95% CI for HR	p-value
Age	1.04	(1.00–1.07)	0.032
Neoadjuvant chemotherapy	0.77	(0.43–1.37)	0.377
Adjuvant chemotherapy	1.92	(0.96–3.84)	0.065
cT stage [§]			
<cT2			
cT2	2.35	(1.24–4.34)	0.007
>cT2	2.20	(0.94–5.15)	0.069
pT stage [§]			
<pT2			
pT2	5.40	(2.24–13.00)	<0.001
>pT2	8.90	(4.35–18.24)	<0.001
pN stage			
N0			
N+	3.50	(1.99–6.15)	<0.001
pM stage			
M0			
M1	2.11	(0.66–6.80)	0.209
Surgical down-staging after chemotherapy [‡]	0.19	(0.02–1.40)	0.102
Thiazolidinedione	1.14	(0.64–2.03)	0.666
b. Multivariate analysis for cancer-specific survival			
	HR	95% CI	p-value
Age	1.01	(0.98–1.05)	0.540
pT stage			
<pT2			
pT2	5.45	(2.24–13.23)	<0.001
>pT2	8.37	(4.00–17.51)	<0.001
Adjuvant chemotherapy	0.88	(0.49–1.60)	0.674
Thiazolidinedione	1.20	(0.66–2.17)	0.548

[§]Clinical and pathologic tumor staging classified according to the 7th American Joint Committee Cancer Staging Manual.

[‡]Surgical and pathologic was defined as the finding of non-muscle-invasive disease (pT1) on RC specimen in patients with muscle invasive disease (cT2) on (TURBT) subsequent to neoadjuvant chemotherapy.

Statistically significant values denoted in bold.