Original Study

Role of Renin-Angiotensin System Blockers on BCG Response in Nonmuscle Invasive, High Risk Bladder Cancer

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Abstract

The best treatment option for high-risk non muscle-invasive bladder cancer is BCG immunotherapy. In this study we looked for potential interaction between drugs with known immunomodulatory effects (angiotensin receptor blockers and ACE-inhibitors) and cancer recurrence in patients treated with BCG. Our results show a benefit in patients treated with angiotensin receptor blockers.

Introduction: The gold standard treatment for high-risk NMIBC is BCG immunotherapy. Some studies suggested an immomodulatory effects for commonly used drugs (ie, ACE-I and ARBs). We aimed to determine whether these drugs impact the prognosis of patients with high-risk NMIBC treated with BCG. **Materials and Methods:** Retrospective analysis on 208 patients from a single academic center with primary high-risk NMIBC treated with transurethral resection followed by 6 weekly instillations of BCG and up to 12 monthly maintenance instillations. ARBs or ACE-I use at the time of treatment initiation was recorded. Inverse probability of treatment weighting (IPTW) was used to adjust for clinical and pathological covariates. IPTW–adjusted Kaplan-Meier curves and weighted Cox proportional hazards regression were used to compare 2-yr failure-free (2-yr FFS), failure-free (FFS), overall recurrence-free (RFS) and progression-free survival (PFS). **Results:** A total of 68 patients were on ACE-I, and 38 on ARBs and treatment respectively. At a median follow-up of 26 months, ACE-I treatment had no significant impact on cancer-related outcomes. Conversely, patients treated with ARBs experienced significant improvements in 2-yr FFS (HR 0.3; 0.1-0.9, $P = .004$), FFS (HR 0.4, 0.1-0.9, $P = .005$), and PFS (HR 0.001; < 0.001-0.001, $P < .001$). No significant impact was found for ARB use in RFS (HR 0.6; $P = .09$). Sensitivity analyses confirmed these results. **Conclusions:** our findings support a potential role of the angiotensin-renin system in bladder cancer development. We identified ARBs as potential beneficial drugs that seems to act in synergy with BCG-immunotherapy.

Clinical Genitourinary Cancer, Vol. 000, No.xxx, 1–7 © 2022 Elsevier Inc. All rights reserved.
Keywords: ACE-inhibitors, Angiotensin receptor blockers, Immunomodulatory, Instillations, Cancer recurrence

Introduction

Immunotherapy with BCG after TURB is the first-line treatment in high-risk NMIBC.[1] The intracavitary instillation of BCG causes an immune-mediated inflammatory reaction, inducing a massive localized response with release of cytokines capable of limiting the development of BCa.[2] Despite its effectiveness, BCG-therapy fails to achieve a long-lasting response in up to 30% to 40% cases.[3]

Secondary immunomodulatory effects have been described in some drugs used for a long time in the treatment of common diseases, such as hypertension.[4] Specifically, agents acting on the RAAS, namely ACE-I and ARBs have been shown to improve survival in patients with metastatic renal cell carcinoma treated with targeted therapy.[5] The RAAS is not only expressed at renal and vascular levels, but also at the level of cancer cells and their microenvironment, where they are thought to play a role in bladder cancer angiogenesis.[6] Other studies suggested an association among this drugs and BCa related outcomes.[7,8] To date, no study directly evaluated the potential immunomodulatory effects of these drugs in NMIBC treated with BCG. Hence, we aim to test separately potential effects of ACE-I and ARBs on BCG related outcomes in patients with high-risk NMIBC.

Materials and Methods

We retrospectively reviewed clinical data identifying patients treated with BCG for high-risk NMIBC at our academic center (Azienda Ospedaliera-Università di Padova) between January 1, 2014 and May 15, 2020. Institutional review board approval was waived because of the retrospective nature of the study, all patients provided written informed consent for data collection. Patients with incomplete clinical or pathological information, as well as subjects treated at other institutions or patients with a previous history of NMIBC on nonurothelial bladder cancer (UC), were excluded. Other exclusion criteria included follow-up time < 3 months and discontinuation of BCG therapy at any time because of intolerance or adverse reactions.

Patients' age at the time of first BCG instillation, gender, BMI, smoking status (current smoker vs. no/previous smoker) and presence of synchronous UTUC were collected. Comorbidities were classified through Charlson Comorbidity Index (CCI).[9] Treatment with either ARBs or ACE-i at the time of treatment start were identified though chart review.

All included patients had first observation high-risk NMIBC and underwent TURB. A second look resection (Re-TURB) was performed 2 to 6 weeks after initial treatment based on pathologic and intraoperative findings in accordance with the physician's indications and current EAU guidelines.[1]

All surgical specimens were processed according to standard pathologic procedures and staged based on the TNM classification by 2 experienced uropathologists. Tumor grade was assigned according to the 2004 World Health Organization system. Pathology variables collected included: tumor histotype (pure UC or UC with variant histology), tumor stage, tumor grade, presence of concomitant carcinoma in situ, presence of multifocal tumor, greatest diameter of the tumor(s) (categorized as < 3cm or ≥ 3cm).

BCG therapy consisted of 6 weekly intravesical instillations (BCG Oncotice) delivered within 6 weeks of the last TURB. Maintenance therapy consisted in monthly instillations; the target duration of maintenance therapy consisted in 12 monthly instillations.

Patients received clinical and radiological follow-up based on EAU guidelines.[1] Every patient underwent cystoscopy examination after the first induction cycle. In case of tumor recurrence with carcinoma in situ after the first induction cycle a second induction cycle was allowed. If urinary cytology was positive but cystoscopy was unremarkable, random biopsies of bladder and prostatic urethra in addition to upper urinary tract workup were performed. During the maintenance course and after that cystoscopy was performed every 3 or 6 months, contrast enhanced imaging yearly, according to guidelines.

Disease recurrence was defined as relapse of high-grade NMIBC or MIBC within 12 months from the last BCG instillation defining failure-free survival (FFS), while recurrence at any time during the follow-up defined recurrence-free survival (RFS). In order to investigate synergic effect of BCG treatment and immunomodulatory drugs, 2-year failure free survival (2-yr FFS) was calculated limiting the follow-up time at 24 months after BCG start, which better approximated the duration of treatment with complete schedule. Progression was defined as tumor relapse at stage T2 or higher in the bladder, thus defining progression-free survival (PFS). Cause of death was attributed through chart or death records reviews. Tumor recurrence in the upper urinary tract was not considered as tumor recurrence but rather as a second primary tumor.

In order to account for baseline differences between patients treated with either ACE-I or ARBs or none of them, IPTW–adjusted analyses were performed based on the Average Treatment Effect (ATE).[10] The propensity to undergo either of the treatment was estimated using a logistic regression model based on age, sex, BMI, CCI, smoking status and presence of concomitant UTUC. Although tumor characteristics were not known or influent for treatment decision, it has been shown that including variables related to the outcomes of interest, even if unrelated to the exposure yield the optimal balancing and reduction of the bias.[11] In light of this tumor histotype, grade, stage, diameter, presence of CIS, multifocality, execution of re-TURB and presence of residual tumor at re-TURB were included in the PS model. PS weights were trimmed below and above the first and 99th percentiles, respectively.[10]

Patient and tumor characteristics were compared between groups pre- and post-weighting using standardized mean differences (SMD).[12] Eventually, FFS, RFS and PFS between treatment groups were compared using IPTW-adjusted Kaplan-Meier curves. We used IPTW-adjusted Cox proportional hazard to calculate the IPTW-adjusted hazard ratios (HR) and 95% confidence intervals (CI) using robust methods.[13] Sensitivity included: an analysis repeating PS estimation without tumor related covariates, this was subsequently adjusted for tumor related variables using multivariable regression models. Secondly, PS estimating the Average Treatment Effect on the Treated (ATT) with boosted regression models was calculated. Lastly, we repeated the analysis including only patients with personal history of hypertension, thus accounting for any potential confounding from the condition itself.

Any P value ≤ .05 was considered statistically significant; all tests were 2-sided. All statistical computations were performed using R Statistical Software (R for Statistical Computing, Vienna, Austria).

Results

A total of 369 patients with complete available data underwent intravesical therapy with BCG at our institution during the study period. 133 patients were excluded because they did not meet the inclusion criteria (28 intolerant to therapy, 15 with follow-up time less than 3 months and 118 with previous history of NMIBC). The final sample consisted of 208 patients.

With a median follow-up of 26 months (IQR 13-43.8), 54 (26%) recurrences, 12 (5.8%) disease progression, 11 (5.3%) deaths and 1 (0.5%) cancer-specific death were reported.

Upon IPTW-adjustment, optimal balance was achieved. In particular the ACE-i sample, resulted in optimal balance except for age (residual SMD 0.23) while the IPTW adjustment on ARBs showed minimal residual unbalance in BMI (SMD 0.13) (Table 1).

Sixty-eight patients reported use of ACE-I. In unadjusted analysis ACE-I use was associated with none of the outcomes of interest. The IPTW-adjusted robust Cox Regression models showed no significant difference for ACE-i use either on 2-yr FFS (HR 1.6, 95% CI 0.8-3; P = .2), FFS (HR 1.3, 0.7-2.3; P = .4) RFS (1.4, 0.8-2.5; P = .3) or PFS (HR 1.4, 0.4-4.5; P = .6) (Table 2). The weighted Kaplan-Meier curves are showed in Figures 1A-D.

Table 1   **Cohort Characteristics Before and After Weighting**

| | Total[1] | ACE-i | | | | | | | ARBs | | | | | | |
| | | Unweighted Sample | | | | Weighted Sample | | | Unweighted Sample | | | | Weighted Sample | | |
		No ACE-I (N = 140)	ACE-I (n = 68)	SMD	P value[b]	No ACE-I	ACE-I	SMD	No ARB (N = 170)	ARB (N = 38)	SMD	P value[a]	No ARB	ARB	SMD
Age in years	71 (65, 76)	69.1	71.1	0.22	.4	69.6	71.8	0.24	69.3	71.9	0.3	.1	69.8	70.2	0.05
Sex: Male	177 (85%)	0.84	0.87	0.02	.7	0.86	0.78	-0.08	0.85	0.87	0.02	1.0	0.85	0.91	0.05
BMI Kg/m^2	26.2 (24.7, 29.1)	26.5	27.8	0.34	.01	27.3	27.3	-0.01	26.6	28.2	0.36	.08	26.9	26.3	-0.14
CCI	1 (1, 2)	1.22	1.85	0.4	.002	1.56	1.41	-0.1	1.32	1.92	0.39	.003	1.43	1.5	0.04
Smoking status: current smoker	32 (15%)	0.16	0.15	-0.01	1.00	0.15	0.14	-0.01	0.16	0.13	-0.03	.8	0.15	0.20	0.05
UTUC: yes	17 (8.2%)	0.89	0.99	0.1	.01	0.92	0.86	-0.06	0.92	0.89	-0.03	.5	0.92	0.94	0.02
Histology: variant	3 (1%)	0.01	0.03	0.02	.3	0.02	0.02	-0.01	0.02	0.0	-0.01	1.00	0.01	0.000	-0.01
Grade: HG	202 (97%)	0.99	0.96	-0.02	.4	0.98	0.98	0.01	0.96	1.0	0.04	.6	0.97	1.0	0.03
T stage = 1	79 (38%)	0.41	0.32	-0.09	.1	0.38	0.34	-0.04	0.38	0.37	-0.01	.7	0.38	0.36	-0.02
Tstage = a	85 (41%)	0.39	0.46	0.07		0.42	0.49	0.07	0.39	0.47	0.08		0.41	0.37	-0.07
Tstage = is	20 (9.6%)	0.07	0.15	0.08		0.09	0.09	-0.01	0.11	0.05	-0.05		0.1	0.13	0.03
Tstage = x	24 (12%)	0.14	0.07	-0.06		0.11	0.08	-0.03	0.12	0.11	-0.01		0.12	0.17	0.06
Dimensio: > 3 cm	76 (37%)	0.36	0.37	0.01	1.0	0.39	0.33	-0.05	0.35	0.42	0.07	.5	0.36	0.3	-0.06
Concomitant CIS: yes	43 (21%)	0.18	0.26	0.09	.2	0.21	0.19	-0.01	0.21	0.18	-0.03	.83	0.21	0.26	0.05
Multifocality: yes	69 (33%)	0.34	0.31	-0.03	.6	0.32	0.4	0.08	0.34	0.32	-0.02	1.0	0.34	0.38	0.04
Re-TURB: yes	127 (61%)	0.61	0.62	0.01	1.0	0.61	0.52	-0.09	0.61	0.63	0.03	.9	0.6	0.54	-0.06
Residual tumor at Re-TURB: yes	41 (20%)	0.18	0.24	0.06	.4	0.2	0.17	-0.03	0.51	0.13	-0.1	.4	0.2	0.2	-0.01

[a] Statistics presented: median (IQR); n (%).
[b] Kruskall-Wallis for continuous variables and Fisher's Exact Test for categorical variables.

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Renin-Angiotensin Blockers and BCG in NMIBC

| Figure 1 | (A): IPTW-adjusted 2-yr FFS curves for ACE-i, (B): IPTW-adjusted FFS curves for ACE-i, (C): IPTW-adjusted RFS curves for ACE-i, (D): IPTW-adjusted PFS curves for ACE-i. |
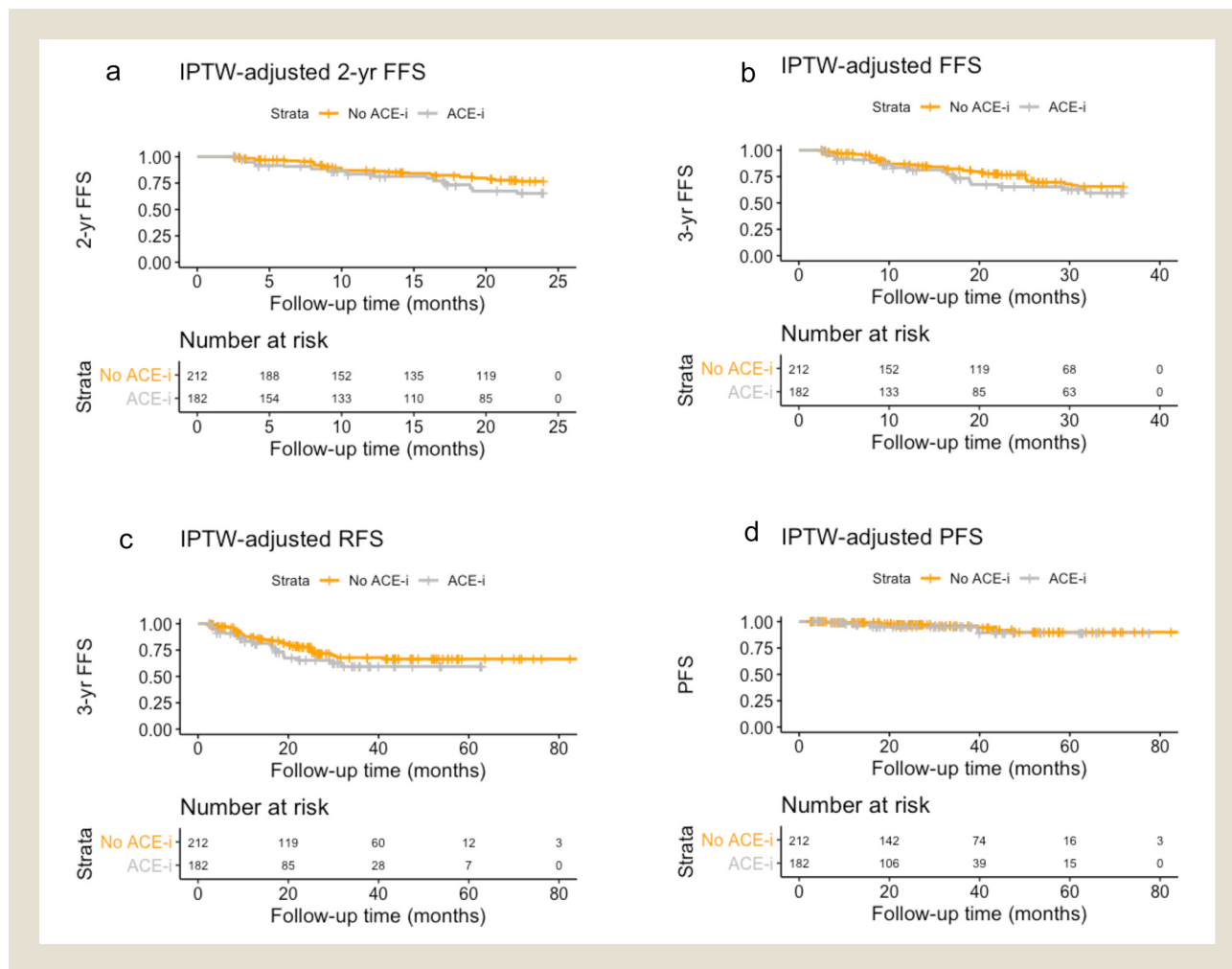
Thirty-eight patients reported use of ARBs. The unadjusted analysis showed a significant association between ARBs use and PFS ($P < .001$). The association with 2-yr FFS, FFS and RFS was not significant, $P = .058$, $P = .08$ and $P = .2$, respectively.

After IPTW-adjustment the regression model showed significant differences for ARB users in 2-yr FFS (HR 0.3; 0.1-0.9, $P = .004$), FFS (HR 0.4, 0.1-0.9, $P = .005$) and PFS (HR 0.001; < 0.001-0.001, $P < .001$). No significant difference was found for ARB use in RFS (HR 0.6; 0.2-1.2, $P = .1$) (Table 2). The weighted Kaplan-Meier curves are showed in Figures 2A-D.

In sensitivity analyses, with regards to the ACE-I, the absence of any association with the outcomes of interest was confirmed (data not shown). In the setting of ARBs use, the association with 2-yr FFS and FFS was confirmed by all the models (all $P < .03$). Specifically, the models including only preoperative variables in the propensity score and later adjusting for pathological covariates and the 1 including only patients with history of hypertension, showed additional significant association with ARBs use and RFS (Supplementary Table 1).

Discussion

In this study we identified a potential beneficial effect of ARBs in synergy with BCG-immunotherapy in patients with high risk bladder cancer, whereas we failed to identify any significant benefit associated with the use of ACE-I.

NMIBC represents a significant challenge for urologists because of the high risk of recurrence and progression, as well as the need for intensive and expensive treatment and follow-up. For high-risk NMIBC, BCG intravesical therapy represents the gold standard treatment[1] even though the drug is not directly targeted to BCa cells but rather acts through multiple pathways involving the immune-system.[2] Multiple commonly prescribed drugs have pleiotropic effects, including immunomodulating effects that could influence the prognosis in different cancers.

In this study we investigated the role of RAAS system, which besides its endocrine functions, stimulates angiogenesis through chronic inflammation, mediated by angiotensin receptor. With specific regards to BCa, Shirotake et al. investigated angiotensin-1 receptor (AT1R) expression and microvessel density (MVD) in

Figure 2 (A): IPTW-adjusted 2-yr FFS curves for ARBs, (B): IPTW-adjusted FFS curves for ARBs, (C): IPTW-adjusted RFS curves for ARBs, (D): IPTW-adjusted PFS curves for ARBs.
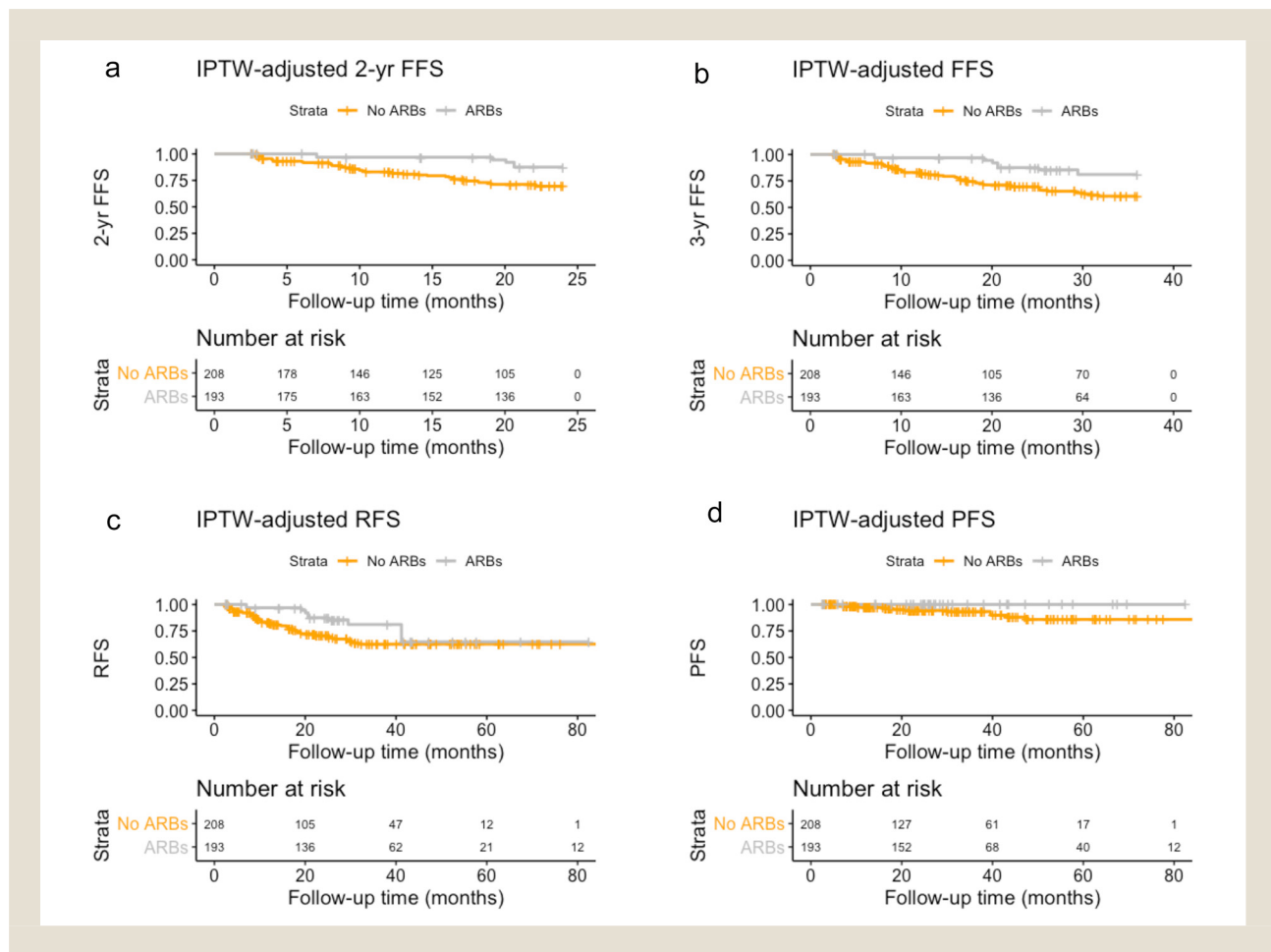
NMIBC and MIBC specimens and showed that MVD increase with stage of disease. Additionally, they found that AT1R was expressed in BCa tumor cells and its expression was greater in MIBC and HG tumors. Moreover, MVD increased with ATR1 expression. Both AT1R expression and MVD were independent predictors of the 1-year RFS, also in patients treated with BCG.[6]

In patients with high stage BCa few studies found positive prognostic association with RAAS system inhibitors. Specifically, RAAS inhibitors reduced CSM and OM in those undergoing RC[14] and metastasis in patients with localized UTUC undergoing nephroureterectomy.[15]

Blute et al. retrospectively analyzed 341 patients with NMIBC undergoing TURB treated with RAAS inhibitors. Multivariable analysis demonstrated that patients treated with BCG (HR 0.68, 95% CI 0.47-0.87, $P = .002$) or ACE-I/ARB (HR 0.61, 95% CI 0.45-0.84, $P = .005$) were less likely to experience tumor recurrence while there was no impact on progression[7]. Similar results were reported by Yuge et al., who showed that ACE-I or ARB use was an independent predictor of tumor recurrence but not stage progression in NMIBC.[8] Despite interesting findings, both these studies had some important limitations since they did not stratify between

ACE-I and ARB users, approximately 50% of patients harbored LG tumors and less than 50 % were treated with BCG with no clear schedule.

In our experience, all patients were EAU high-risk NMIBC and all of them were treated with appropriate BCG schedule and strict follow-up. On IPTW analysis we could identify a significant difference between the 2 major classes of drugs acting on the RAAS system. Specifically, ACE-I use did not impact both on short term and long-term outcomes. On the other hand, the use of ARBs provided significant benefit on BCG failure both concomitant and after 12 months from the last instillation. Additionally, no cases of progression were observed in patients treated with ARBs while we could not identify significant impact on long term recurrences.

Our findings somehow confirm the findings of the aforementioned studies, suggesting a potential role of RAAS system in the NMIBC pathways. In addition, we could identify ARBs as the major factor involved and confirm its association in patients treated with BCG. The apparently contrasting findings regarding FFS and RFS in ARBs users could be explained by a potential synergic effect of the drugs during BCG therapy, that might end after discontinuation of instillations and might suggest a longer duration of the maintenance

Table 2 Models Comparing Outcomes Between Users and Nonusers of ACE-I and ARBs

| | ACE-i | | | | | ARBs | | | | |
| | | Unadjusted Analysis | | Adjusted Analysis | | | Unadjusted Analysis | | Adjusted Analysis | |
	Events N (%)	HR (95% CI)	P value	HR (95% CI)	P value	Events N (%)	HR (95% CI)	P value	HR (95% CI)	P value
2-yr FFS	20 (29.4)	1.67 (0.93-3.0)	.08	1.58 (0.85-2.94)	.2	4 (10.5)	0.37 (0.13-1.04)	.058	0.32 (0.11-0.91)	.004
FFS	22 (32.4)	1.39 (0.82-2.38)	.23	1.32 (0.74-2.34)	.4	6 (15.8)	0.47 (0.2-2.11)	.08	0.35 (0.14-0.87)	.005
RFS	22 (32.4)	1.5 (0.87-2.58)	.1	1.41 (0.79-2.52)	.3	7 (18.4)	0.59 (0.27-1.3)	.2	0.55 (0.25-1.23)	.09
PFS	5 (7.4)	1.76 (0.55-5.58)	.3	1.36 (0.41-4.5)	.6	0 (0)	< 0.01 (< 0.01-0.01)	.001	< 0.01 (< 0.01-0.01)	.001

schedule. This interpretation is consistent with the hypothesis of an immunomodulating effect of the drugs on the action of BCG.

The reason for this difference between ARBs and ACE-I remains to be determined. Kosugi et al. have shown that the specific blockade of the AT1-R by ARBs prevents angiogenesis in human BCa in vitro and the growth of these cells in in vivo xenograft. Specifically, it was observed that angiotensin II induces the secretion of pro-angiogenic cytokines VEGF and IL-8 in neoplastic bladder cells and that this production was instead suppressed by candesartan. Further studies are needed to prove this hypothesis.[16] Based on the data of Shirotake, it can be assumed that patients with higher AT1R and MVD expression tend to relapse despite standard therapies and are the best candidates for AT1R antagonist therapy.[6]

Recently Strauss et al. presented the preliminary results of their study were patients treated with ARBs responded better to anti PD(L)1 immunotherapy in various cancer and again, this advantage was maintained in comparison with ACE-i. The authors hypothesize that the selectivity of ARBs in blocking AT1R potentially work better at lowering VEGF and TGF-β than inhibition of angiotensin-converting enzyme.[17]

In light of this we could hypothesize that the direct action of ARBs on the receptor could exert a more powerful synergic effect with BCG-therapy rather than the inhibition of Angiotensin II formation. More specific molecular studies are needed to explain this difference.

The strengths of our findings come from the homogeneity of our cohort. Every patient included underwent treatment and follow-up at a tertiary academic institution, specimens were analyzed by dedicated uropathologists and BCG was administered with a consistent schedule. We chose to include only EAU high-risk patients because this population is the one that might benefit the most from the immunotherapy and we restricted the sample to first observation NMIBC to avoid any potential bias. Thus, excluding the recurrence-rate, all the EORTC and CUETO covariates were collected and used in the PS model, together with clinical characteristics in order to compare similar pseudo-populations that differ only for the drug of interest.

Our study is not devoid of limitations which are mainly inherent to its retrospective design. Although PS and IPTW aim to remove the effects of confounders, there could be a residual bias coming from the data collected retrospectively. In order to overcome these limitations, we performed several sensitivity analyses that confirmed and somehow extended our findings. Some information (such as the precise dosage, frequency and duration of therapy with the drugs of interest) are not always easily verifiable through medical records. In order not to affect the results, we decided to dichotomously classify the use of drugs on the basis of use/not-use. The follow-up period is relatively short, with a median of 26 months (starting after the first BCG instillation). However, in our opinion this follow-up time is sufficient to focus on the synergistic effects of drugs on BCG therapy. In fact, we chose as one of the endpoints 2-yr FFS in order to approximate the longest duration of BCG course in our institution (6 weekly + 12 monthly + 4 weeks waiting time between last instillation and cystoscopy). The determination of any long-term benefits requires further studies that include longer follow-up periods.

Although no definitive conclusion can be made with the level of evidence reported in this study, these findings may open a new field of research, investigating both this effect on larger and different population and its mechanisms of action.

Conclusions

ARB therapy improved the efficacy of BCG therapy in patients with high-risk NMIBC, specifically preventing early recurrence during the instillation schedule. Previous studies showed a potential impact of the RAAS in BCa, we could discriminate the effects between ARBs and ACE, with the latter not providing significant benefit. Further basic science research is needed to determine the exact mechanism of action that these medications and interventional studies could provide higher level evidence of a potential, affordable, boost to BCG-efficacy.

Clinical Practice Points

- BCG endocavitary therapy is to date the gold standard treatment for high risk non muscle-invasive bladder cancer, acting through an immune-mediated mechanism. Several commonly used medications have been found to have secondary immunomodulatory effects, in particular some basic science research suggest a potential interaction between antihypertensive agents such as angiotensin receptor blockers (ARBs) and angiotensin converting enzyme inhibitors (ACEi) and BCG action.
- In this single center retrospective study, we identified a potential beneficial effect of ARBs in synergy with BCG-immunotherapy, thus preventing short term recurrences.
- Despite the limitations given by the retrospective study design, our findings are meaningful since they can stimulate further research in a topic where little advances were made in recent years, suggesting a potentially cost-effective and well tolerated enhancing of BCG therapy.

Research Involving Human Participants and/or Animals

This research study was conducted retrospectively from data obtained for clinical purposes.

Code Availability (Software Application or Custom Code)

Statistical code available upon request.

Disclosure

The authors declare that they have no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clgc.2022.02.007.

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