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Efficacy and Safety of a 5-Alpha Reductase Inhibitor, Dutasteride, Added to Bacillus Calmette-Guérin Immunotherapy for Prevention of Recurrence and Progression of Intermediate- and High-Risk Non-Muscle Invasive Bladder Cancer: A Single-Arm, Phase 2 Clinical Trial

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What's known on the subject? and What does the study add?

Androgens and receptor analyses, which constitute an important step in cell growth and differentiation, play a role in bladder cancer. Anti-androgen therapies have a positive effect on bladder tumors. Studies showed 30% decrease in the recurrence of bladder cancer among patients treated with 5α-R type-1/2 inhibitor. Dutasteride failed to show predicted efficacy in recurrence of bladder cancer. However the decrease in recurrences after the 6th month of dutasteride treatment and the fact that the lack of progression during the treatment is promising for future studies.

Abstract

Objective: To assess the efficacy and safety of 5α-R inhibitor dutasteride added to standard Bacillus Calmette-Guérin (BCG) immunotherapy for preventing recurrence and progression in intermediate- and high-risk non-muscle invasive bladder cancer (NMIBC).

Materials and Methods: Patients received BCG immunotherapy in accordance with the European Association of Urology guidelines and dutasteride (0.5 mg) tablet were orally administered once a day. The participants were monitored for recurrence or progression for 24 months. Androgen receptor expression assay was performed on cystoscopic biopsy materials. According to the data from retrospective studies of patients with bladder cancer, the recurrence rate was 50% in patients with BCG immunotherapy without dutasteride, and 25% in those given dutasteride, with 23 patients included in the study.

Results: A total of 14 (60.9%) patients could finish the follow-up. Ten patients completed the 24 months follow-up without recurrence and 4 patients had recurrence. Nine (39.1%) patients failed to complete the follow-up. Of these patients, 28.5% had recurrence. No patient progressed to MIBC and no low-grade tumor progressed to high grade. There was no statistical significance between recurrence and non-recurrence groups for AR mRNA, ARV7 mRNA, AR protein and ARV7 protein expression. But all expressions were higher in the non-recurrence group.

Conclusion: Dutasteride failed to show predicted efficacy in recurrence in this prospective study, most likely due to the limited number of patients, however the decrease in recurrences after the 6th month of dutasteride treatment and the fact that the lack of progression during the treatment is promising for future studies.

Keywords: Bladder cancer, dutasteride, recurrence

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Introduction

Bladder cancer is the ninth most common malignancy and the thirteenth most common cause of cancer death in the world (1). Intravesical instillation of Bacillus Calmette-Guérin (BCG) is recommended after transurethral resection for intermediate- and high-risk non-muscle invasive bladder cancer (NMIBC) (2). Despite treatment, approximately 15-61% of NMIBC recur and 1-45% of NMIBC progress to muscle invasive bladder cancer (MIBC) (3). When MIBC develops, disease-related survival decreases and the treatment burden increases. Numerous clinical trials have focused on preventing NMIBC progression and recurrence.

Kourbanhoussen et al. (4) showed that anti-androgen therapies have a positive effect on bladder tumors in a systematic review. Moreover, in a prospective study, 5-alpha reductase (5α-R) type-2 inhibitor finasteride treatment was associated with decreased bladder cancer incidence (5). A retrospective study based on the findings of this prospective study suggested up to 30% decrease in the recurrence of bladder cancer among patients treated with 5α-R type-1/2 inhibitor, dutasteride (6). Dutasteride is a safe oral medication commonly used to treat benign prostatic hyperplasia (BPH). Many studies have revealed that androgen receptor (AR) expression in prostate cancer is associated with increased tumor progression (7). Also, some studies have found that AR expression was significantly associated with bladder cancer recurrence (8).

Although it was demonstrated in a retrospective study that dutasteride reduced the recurrence of intermediate- and high-risk NMIBC, to the best of our knowledge, there is no prospective clinical study focusing on dutasteride along with BCG immunotherapy. Furthermore, there is no evidence suggesting that the AR expression in recurrent and invasive bladder cancers is correlated with the therapeutic efficacy of dutasteride. Therefore, we designed a single-arm, single-center, phase 2 clinical trial to assess the efficacy and safety of 5α-R inhibitor, dutasteride, added to standard BCG immunotherapy for preventing recurrence and progression of intermediate- and high-risk NMIBC.

Materials and Methods

Overall Design

This single-arm, single center, open-label phase 2 clinical trial was designed to evaluate the efficacy and safety of dutasteride for preventing recurrence when added to BCG immunotherapy, which is used in the standard for intermediate- and high-risk NMIBC treatment. The patients received BCG immunotherapy in accordance with the European Association of Urology (EAU) guidelines and dutasteride (0.5 mg) tablet were orally administered once a day. Participants were regularly surveilled with cystoscopy every 3 months and thoracoabdominal computed tomography once a year in accordance with American Urology Association (AUA) and EAU guidelines. The participants were monitored for recurrence or progression for 24 months. The primary endpoint was the detection of recurrence because of cystoscopy. Secondary endpoints include observation of bladder tumor invasion into bladder muscle on cystoscopic biopsy material and determination of the relationship between AR expression and treatment efficacy. AR expression assay was performed on cystoscopic biopsy materials. This study was approved by the Local Ethics Committee (Dokuz Eylul University approval number: 2017/09-3, date: 18.05.2017).

Eligibility Criteria

Male patients older than 18 years old with primary intermediate- and high-risk NMIBC were eligible.

Exclusion criteria;

Patients with the Eastern Cooperative Oncology Group performance status 3 or more,

Patients with prior BCG or other intravesical treatment, radiotherapy to the pelvic area, or immunosuppressive disease,

Patients with prior malignancy within the previous 5 years, except for those with localized curable cancers such as basal or squamous cell skin cancer,

Patients ineligible to receive BCG or dutasteride,

Patients with serious medical conditions or psychiatric illnesses that may limit their ability to adhere to study protocol.

Quantitative Polymerase-Chain Reaction (qPCR) Analysis of AR-FL and AR-V7

Bladder cancer tissue samples were excised by transurethral resection, transferred immediately to Ribosave (Bio-Speedy, BS-NA-203-250), snap frozen in liquid nitrogen, and stored at -20 °C. Total RNA isolation from tissue samples was performed using a RNeasy Mini kit (Qiagen 74104) according to the manufacturer's instructions. RNA concentration and purity were checked by NanoDrop 1000 spectrophotometer following isolation (Thermo, US). An amount of 500 nanograms of RNA per sample was used for cDNA synthesis with the RevertAid First Strand cDNA Synthesis kit (Thermo, K1622) according to the manufacturer's instructions. cDNA synthesis was carried out in an Applied Biosystems, SimpliAmp Thermal Cycler. For AR-FL or AR-V7 primer evaluation, 10 or 20 ng of cDNA of each sample was applied per PCR, respectively. The Johns Hopkins Group adjusted the PCR reaction parameters for primers from the original Antonarakis et al. (9) publication. PCR primer pairs used for PCR targeted AR-FL fw-

CAGCCTATTGCGAGAGAGCTG, rev-GAAAGGATCTTGGGCACTTGC), AR-V7 (10) fw-CCATCTTGTCGTCTTCGGAAATGTTA, rev-TTTGAATGAGGCAAGTCAGCCTTTCT), and GAPDH (fw-GAAGGTGAAGGTCGGAGTC, rev-GAAGATGGTGATGGGATTTC). qPCR was performed using SYBR-Green fluorescent dye (Ampliqon, A323406) in an Applied Biosystems 7500 Fast Real-Time PCR Detection System. The samples were examined in quadruplicate. Relative gene expression of AR-FL and AR-V7 was normalized to GAPDH using the $2^{-deltaCT}$ method.

Western Blotting of AR-FL and AR-V7

Bladder cancer tissue samples were excised by transurethral resection, snap frozen in liquid nitrogen, and stored at -85 °C. Tissue samples were homogenized in an ice-cold modified RIPA buffer containing complete ultramini protease inhibitor cocktail (Roche 05892970001) and phosSTOP (Roche) using pestles (Tmomas Scientific, 1226C62) as described before (11). The homogenate was centrifuged at 15.000 x g for 20 min at +4 °C. Protein lysates were prepared and analyzed as described before (ref1) using 80 micrograms of protein. Blots were incubated with the following primary antibodies at indicated dilutions: Mouse anti AR-FL (sc-7305), 1:200, Mouse anti-AR-V7(Precision Antibody, AG10008) 1:500, rabbit calnexin (sc-11397), 1:5000. Proteins were detected using fluorescence-conjugated secondary anti-mouse (Licor 800CW: IRD 926-322-10) or anti-rabbit (Licor 680 RD: 926-68071) antibodies both at 1:15000 and Chemidoc MP Imaging System (Biorad). Equal loading and transfer were confirmed by repeat probing for Calnexin. Band intensities were quantified as pixels using ImageJ software (NIH).

Outcome Measures, Planned Sample Size and Statistical Analysis

According to the data from retrospective studies of patients with bladder cancer, the recurrence rate was 50% in patients with BCG immunotherapy without dutasteride, and 25% in those given dutasteride, with 80% power (Beta=0.20) and alpha=0.05, assuming 23 patients were included in the study (6,12,13). Less than 25% of this patient group were predicted to experience recurrence. The patients were divided into two groups as those with and without recurrence. The groups were compared in terms of general demographic data and tumor characteristics with Fisher's Exact test. The normality of AR-FL protein, AR-V7 protein, AR-FL mRNA and AR-V7 mRNA expression between the two groups was evaluated with histogram, the coefficient of variation, Skewness-Kurtosis, detrended normal Q-Q plot and Shapiro-Wilk test, and they all did not fit the normal distribution. The two groups were compared with the Mann-Whitney U test, using the statistical differences of two non-parametric-dependent samples. Data were analyzed using SPSS version 22.0 (SPSS, Chicago, IL, USA). The p-value was taken as $p<0.05$ for significance.

Results

A total of 23 patients were included in the study; 14 (60.9%) could finish the follow-up. Ten patients completed the 24 months follow-up without recurrence and 4 patients had recurrence. Nine (39.1%) patients failed to complete follow-up (2 patients were excluded by the investigator, 1 patient was unable to continue due to BCG side effects and 6 patients withdrew) (Figure 1). Recurrence was present in 28.5% of the patients. Dutasteride failed to show effectiveness for recurrence. No patient progressed to MIBC and no low-grade tumor progressed to high grade. The median age of the patients was 67 years and the median tumor size was 40 mm. The median EORTC recurrence risk score and CUETO recurrence risk score were 6 and 4, respectively. Baseline characteristics of the patients are shown in Table 1. There was no statistical significance between recurrence and non-recurrence groups for demographic and pre-treatment parameters (Table 2). There was no statistical significance between recurrence and non-recurrence groups for AR mRNA, ARV7 mRNA, AR protein and ARV7 protein expression. But all expressions were higher in the non-recurrence group (Table 3).

Discussion

The most effective treatment for preventing recurrence and progression in NMIBC is intravesical BCG immunotherapy. Despite treatment in intermediate- and high-risk bladder cancer, up to 50% recurrence and 10-15% progression are observed. In retrospective studies of patients taking 5α-R inhibitors, recurrence rates were found to be 50% less in those with concomitant NMIBC. In a study conducted in patients receiving finasteride, the recurrence of bladder cancer decreased by 36%, and this effect was seen in Whites and Hispanics, but not in Black races (13). This demonstrates the importance of prospective studies in specialized groups for the standardization of retrospective studies in large patient groups. The effects of genetics, drug interactions and environmental factors were more evident in small groups. Also, smoking, occupational exposure and herbal products affect the outcomes.

The time when the drug should be started to see the effect is an important question for 5α-R inhibitor treatment for bladder cancer. Mäkelä et al. (14) found that 5α-R inhibitors improved disease-specific survival in 10,720 Finnish men with bladder cancer. Moreover, these benefits were seen both with use before and after bladder cancer diagnosis. In this study, the drug was started after diagnosis. There is a need for studies with more samples about the optimal drug dose and duration. In our study, since 3 of the 4 patients with relapse occurred in the first 3 months, it can be considered that more than 3 months is required for the optimal effect. Additionally, 6 months of treatment is

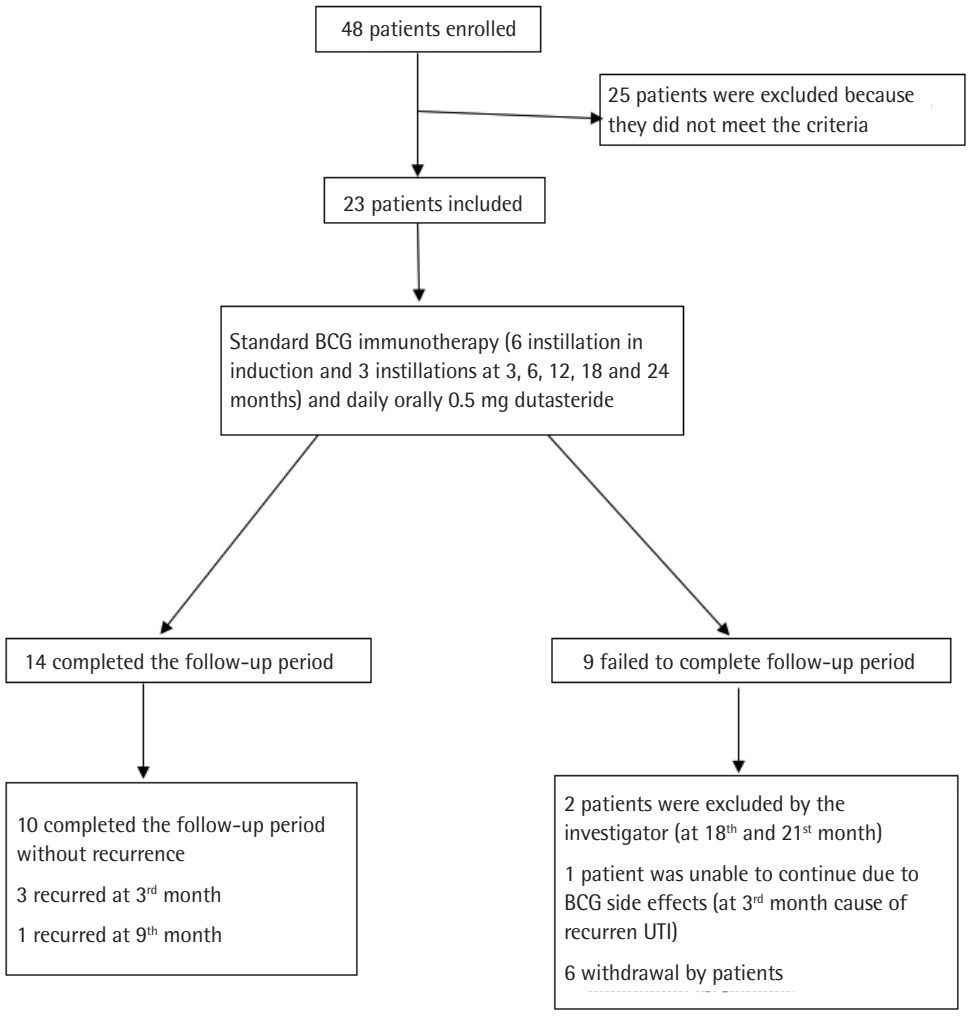

Figure 1. Patients overview

required for optimal effects for treating BPH (15). If we had created a protocol to evaluate the efficacy of dutasteride after the 6th month of treatment, our recurrence rate would have been 9% (per protocol) (4% according to intention to treat analysis). The recurrence of only 1 patient after 6 months makes it questionable that dutasteride may be an alternative treatment together with BCG, although statistical significance was not obtained.

Another expected outcome of intravesical BCG therapy is the prevention of progression. Despite BCG treatment, progression to 5-10% MIBC is observed in two-year follow-ups (16). At the 5-year follow-up, the progression reached 40% in some series. Tumor grade progression is expected to be 3% over 2 years (17). In this study, in addition to the absence of muscle invasion in any patient, the absence of stage and grade progression was interpreted as the effect of dutasteride.

McMartin et al. (18) found that the use of 5α-R inhibitors before cystectomy was associated with better overall survival, lower proportion of positive margins and lymphovascular invasion. Shiota et al. (6) found that androgen suppression therapy (androgen deprivation therapy for prostate cancer or dutasteride for BPH) lowered the risk of bladder cancer recurrence. Wang et al. (19) found that 5α-R inhibitors decreased the risk of bladder cancer-related death, but there was no significant difference in the recurrence rate. In this study, no effect on the 2-year mortality was observed. Additionally, how long and at which dosage the 5α-R inhibitor should be taken for reduced mortality could not be explained.

Many studies have been conducted on AR expression and its effects. While some studies have identified an association between AR positivity and tumor progression (20), some studies reported that high AR expression is associated with lower recurrence and better disease outcome (21). In this study, AR and AR-V7 mRNA and protein expressions were lower in the group with recurrence, but no statistically significant difference was detected. AR expression is affected by genetics, drug

use and many other factors (22). The lack of a standard for expression analysis and the fact that the factors mentioned are not homogenized cause different outcomes. In some studies, immunohistochemical methods were used and the required rate for positivity was between 1 and 30%. In the other group, RT-qPCR was used. In this respect, the standardization of positive tissues with different methods cannot be done at this stage. But tumors expressing AR are likely to respond better to 5α-R inhibitors and have a better prognosis.

Urinary tract infection and upper respiratory tract infection constituted most adverse events, while serious adverse events were reported as urethral stenosis, coronary artery disease and dyspnea. Adverse events are generally seen to be related to BCG. Sexual adverse effects are the most common side effects

Table 1. Baseline characteristics of the patients

Characteristic	n (%)
Number of patiens	23 (100)
Age	
>65	14 (60.9)
<65	9 (39.1)
Tumor stage	
pTa	15 (52.2)
pT1	7 (43.5)
pT1+	1 (4.3)
Tumor grade	
Low grade	13 (56.5)
High grade	10 (43.5)
Concurrent CIS	
Yes	2 (8.7)
No	21 (91.3)
Number of tumors	
Single	6 (26.1)
Multiple	17 (73.9)
Tumor size	
<3 cm	7 (30.4)
>3 cm	16 (69.6)
EAU risk group	
Low	0 (0)
Intermediate	13 (56.5)
High	10 (43.5)

CIS: Carcinoma *in situ*, EAU: European Associaton of Urology

Table 2. Recurrence status according to demographic and pre-treatment parameters of patients

Variables n (%)	Groups		p-value
	Non-Recurrence (10)	Recurrence (4)	
Age >65	7 (70%)	1 (25%)	0.175
BMI >25	9 (10%)	2 (50%)	0.176
Tumour >3 cm in diameter	8 (80%)	2 (50%)	0.311
Multiple tumour	6 (60%)	4 (100%)	0.210
Concomitant CIS	1 (10%)	0 (0%)	0.714
High grade tumour	3 (30%)	2 (50%)	0.455
T1 tumour	2 (20%)	2 (50%)	0.311
EORTC high risk	3 (30%)	2 (50%)	0.455

Fisher's Exact test was used for statistical analysis between groups. BMI: Body mass index, CIS: Carcinoma *in situ*, EORTC: European Organisation for Research and Treatment of Cancer

Table 3. AR-FL protein, AR-V7 protein, AR-FL mRNA, AR-V7 mRNA, AR-FL/AR-V7 protein, and AR-FL/AR-V7 mRNA expressions according to recurrence groups

Variables Median (min-max)	Groups		p-value
	Non-Recurrence (10)	Recurrence (4)	
AR-FL protein	0.53 (0.6-2.4)	0.31 (0.6-0.87)	0.374
AR-V7 protein	1.49 (0.2-4.32)	1.06 (0.87-14.23)	1.0
AR-FL mRNA	0.049 (0.0006-0.29)	0.015 (0.004-0.034)	0.188
AR-V7 mRNA	0.000089 (0.000007-0.00044)	0.000035 (0.000007-0.000079)	0.106
AR-FL/AR-V7 protein	0.39 (0.09-1.62)	0.28 (0.004-0.91)	0.539
AR-FL/AR-V7 mRNA	449 (52.6-1168.3)	343.42 (90.7-3377.6)	1.0

Mann-Whitney U test was used for statistical analysis between groups. AR-FL: Full-length androgen receptor, AR-V7: Androgen receptor splice variant 7

from 5α-R inhibitors (0.9-24.0%). Of these, the most common is erectile dysfunction, which is followed by ejaculatory dysfunction and decreased libido (23). Some studies have shown increased depression with 5α-R inhibitors, but there was no direct link found (24). Moreover, studies failed to demonstrate an increased risk of suicide (25). Adverse effects related to dutasteride were not reported by patients. Erectile dysfunction, one of the most important side effects of dutasteride, was not a complaint questioned and prioritized by the patients in this group.

Study Limitations

Dutasteride failed to show a predicted efficacy for recurrence in this prospective study. The difficulties experienced in the follow-up period during the COVID-19 pandemic, 6 patients withdrew from the study. The small number of patients who could complete the study may be the most important limitation.

Conclusion

Androgens and receptor analyses, which constitute an important step in cell growth and differentiation, play a role in bladder cancer. In our study dutasteride failed to show predicted efficacy in recurrence in this prospective study, most likely due to the limited number of patients. However, the decrease in recurrences after the 6th month of dutasteride treatment and the fact that the lack of progression during the treatment is promising for future studies.

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Ethics

Ethics Committee Approval: This study was approved by the Local Ethics Committee (Dokuz Eylul University approval number: 2017/09-3, date: 18.05.2017).

Informed Consent: Signed informed consent was collected from all subjects.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.D.D., C.İ., S.Ö., G.E., V.Ş., A.A.E., Concept: M.D.D., H.A.Y., A.E.S., G.E., V.Ş., A.A.E., Design: M.D.D., H.A.Y., C.İ., S.Ö., A.E.S., G.E., Y.T., V.Ş., O.B., A.A.E., Data Collection or Processing: M.D.D., H.A.Y., G.E., Y.T., V.Ş., A.A.E., Analysis or Interpretation: M.D.D., H.A.Y., S.Ö., G.E., Y.T., O.B., A.A.E., Literature Search: M.D.D., C.İ., S.Ö., A.E.S., G.E., Y.T., V.Ş., O.B., A.A.E., Writing: M.D.D., H.A.Y., C.İ., S.Ö., A.E.S., G.E., Y.T., V.Ş., A.A.E.

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