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Possible Role of 5-Alpha Reductase Inhibitors in Non-Invasive Bladder Urothelial Neoplasm: Multicentre Study

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Reviewer no. 1==========

General comment (originality, scientific accuracy, strengths and/or weaknesses): An original work, I think as the first work done in this field, will open up new horizons. length of the article, discussion is sufficient, there may be a lack of material method part, but I ignore it.

Major corrections (main criticisms): I congratulate the authors

Minor corrections (page, paragraph, line where the author must make the corrections): I think it can be published without any changes

Answer: Thanks for your revision and all your compliments about our paper. We hope taht our study might represent the first step to investigate the role of androgens in bladder cancer.

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Reviewer no. 2

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General comment (originality, scientific accuracy, strengths and/or weaknesses): The authors assess the effect of 5-ARIs on the recurrence of NMIBC showing that patients receiving 5-ARIs has lower recurrence rate with lower grade tumors. The main strength of the current study is the scarce data about this topic in the literature and the main weakness is the retrospective nature of the study and the abscence of female patient.

Answer: Thanks for these comments, certainly, we do completely agree with you about the retrospective nature of this study and the absence of female subjects. Unfortunately this drug category (5ARIs) is off label, as you surely know, for females.

Major corrections (main criticisms):

1- Please update the reference list for example Reference number 1 can be updated to the most recent publication "Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries" published in 2018

Answer: Thanks for this important suggestion, following your advice we add this up-to-date reference for the epidemiology of bladder cancer.

2- In the discussion, I suggest that authors report the results of similar studies and compare it with their study like "PMID: 27506696", Furthermore, there is a recent published study that showed that Finasteride doesn't prevent bladder cancer it will be interesting if it is added in the discussion "PMID: 29731413"

Answer: Thanks for this important suggestion. The first paper by Shioto et al,, was already discussed within the manuscript and the reported data support our results . About the second suggested paper by Sathianathen et al. (“Finasteride does not prevent bladder cancer: A secondary analysis of the Medical Therapy for Prostatic Symptoms Study”) the overall incidence of bladder cancer was very limited, resulting in only 18 patients (0.8%) The Authors concluded that there was no difference in the incidence of bladder cancer between men who received finasteride and those who did not (0.74% vs. 0.61%, p = 0.67). Sincerely, due to the bias of this study (i. e. lack of data on

potential confounders, for example, smoking history), and to the limited number of patients with bladder cancer we did not added this study in the discussion section.

Minor corrections (page, paragraph, line where the author must make the corrections): Please add table 1 in the study and not as a supplementary material

Answer: As correctly suggested, we add the Table 1 at the end of the manuscript.

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Reviewer no. 3

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General comment (originality, scientific accuracy, strengths and/or weaknesses): Thank you very much for the opportunity to review your manuscript, of the study about association between 5-alpha reductase inhibitors and bladder cancer. In 2014, Izumi et al first reported bladder cancer (BC) recurrences under androgen deprivation therapy (ADT) in prostate cancer (PC) patients were significantly lower than PC without ADT. Thereafter Shiota et al reported that not only ADT, but also androgen suppression therapy with 5-alpha reductase inhibitors reduced BC recurrence. The authors collected as much as 423 BC patients from Italian multicenter and drew a similar conclusion to the previous studies. This study is significant in that it dealed with relatively more cases than the previous studies.

Major corrections (main criticisms): You need to do multivariate analysis to adjust multiple confounding risk factors to evaluate the effect of 5-alpha reductase correctly.

Minor corrections (page, paragraph, line where the author must make the corrections): None.

Answer: Thanks for your revision. As you correctly suggested, we have updated the manuscript with the univariate and multivariate analysis focusing on the risk of recurrences. We described the multivariate analysis in statistics section and we inserted a second Table (Table 2) containing the analysed data. Thanks again for this important suggestion, which allowed to better support our results.

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Scheda di revisione editoriale

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Tabelle: Si prega di spostare la tabella al fondo del file del manoscritto.

Figure: Si prega di specificare le didascalie delle figure inserendole al fondo del file del manoscritto.

Possible Role of 5-Alpha Reductase Inhibitors in Non-Invasive Bladder Urothelial Neoplasm: Multicentre Study

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Running title: 5 ARIS in NMIBC

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Abstract

BACKGROUND: About 75% of urothelial bladder cancers are non-muscle invasive (NMIBC), and limited to mucosa (Ta or CIS) or sub-mucosa (T1). An increase of androgen expression and androgen receptors has a positive effect on oncogenic expression. We aimed to evaluate whether 5-alpha reductase inhibitors (5-ARI) have a role in NMIBC.

METHODS: We retrospectively evaluated the clinical and pathological data of 423 patients with NMIBC who underwent transurethral bladder resection. We analysed the number of resections, number of total recurrences, time of recurrences, and histopathology details. The population was classified into two groups: treated and untreated with 5-ARIs. The enrolled patients were in treatment with 5ARIs for symptomatic prostatic hyperplasia for at least 12 months. Mean follow-up time was 30.43 months.

RESULTS: Patients treated with 5-ARIs had a lower rate of recurrence (14%) than the untreated group (37%). There was a significant difference in the mean number of recurrences between the untreated and the treated group (p value: 0.006). Furthermore, the treated group showed a significantly greater number of low than high grade tumours, compared to the untreated group (p value $\leq$ 0.05). There was a significant decrease in the number of muscle invasive tumours in treated patients (p value = 0.032). The recurrence-free survival rate of patients treated with 5-ARIs was significantly higher (p value: 0.0001).

CONCLUSIONS: Long-term treatment with 5- ARIs might reduce the risk of bladder tumour recurrence, extension of lesions and increase the recurrence-free survival rate. A long-term, randomized prospective study could definitively assess the possible role of these drugs.

Keywords: bladder cancer, 5 alpha reductase inhibitors, TURB, NMIBC

INTRODUCTION

Bladder cancer (BC) represents the seventh most prevalent malignant disease in the male population in the world, and the eleventh in both genders. In the European Union the age-standardised incidence rate is 19.1 for men and 4.0 for women [1].

It is the thirteenth most common cause of cancer death. The most common BC type is transitional cell carcinoma, also called urothelial carcinoma. Approximately 75% of patients with BC present with a disease confined to the mucosa (stage Ta, CIS) or submucosa (stage T1); in younger patients (< 40 y.o.) this percentage is even higher [2]. Patients with Ta, T1 and CIS have a higher prevalence (due to long-term survival in most of cases) and lower risk of cancer-specific mortality when compared to T2-4 tumours [1, 3].

These tumours often recur, and in about 20% of cases, progress to high grade muscle-invasive BCa (MIBC), which is more likely to develop metastases [4]. Intravesical recurrence and progression to invasive cancer seems to be linked to the number of bladder lesions, tumour grade, tumour stage and concomitant presence of carcinoma in situ (CIS) [5-7]. The common risk factors of urothelial cancer include aging [8], smoking history [9], medications, occupational exposures, water arsenic, *Schistosoma haematobium* infection, irradiation [10], and genetic factors [11]. Male gender is also a well-known risk factor, supported by evidence in numerous pre-clinical studies showing the involvement of androgen receptor (AR) signalling in bladder carcinogenesis and bladder cancer growth [12, 13]. This seems to be confirmed by a decreased incidence of primary bladder cancer after androgen-deprivation therapy (ADT) compared with surgical therapy and radiotherapy for prostate cancer [14]. In the male population, the high prevalence of benign prostatic hyperplasia (BPH) with lower urinary tract symptoms, has led, over the years, to a widespread use of 5α-Reductase inhibitors (5-ARIs).A reduced incidence of bladder cancer with 5-ARIs has been reported, linked to the catalization of testosterone into dihydrotestosterone, which is 10-fold more potent than testosterone [15]. Similarly, Izumi et al. also reported an inhibitory effect of Androgen-suppression therapy (AST) on the occurrence and recurrence of bladder cancer [16]. Currently, in the literature, a limited number of studies evaluate the effect of 5-ARIs administered for BPH on bladder cancer recurrence. In this retrospective study, we examine the behaviour of non-muscle invasive bladder cancer (NMIBC) in male patients in treatment with or without 5-ARIs.

MATERIALS AND METHODS

This retrospective study evaluated 423 patients with previous NMIBC who underwent transurethral resection of bladder (TURB) for the first time between January 2015 and June 2017. Data analysis was performed in December 2018 to achieve at least 18 months of follow up. The study was performed in accordance with the Ethical Principles for Medical Research Involving Human Subjects (World Medical Association, The Declaration of Helsinki Principles, 2000). Data were collected through a careful analysis from the archives of three Urology departments. Of the 423 evaluated patients, we excluded patients with a lack of data regarding personal therapy (51), a lack of histopathological reports (12), those lost during follow-up (38) and those with squamous cell carcinoma components (10). The study was conducted on 312 patients and the following parameters were considered: age, smoking habits, histopathological data and median follow-up (Table 1). Regarding patient's medication, particular attention was paid to use of dutasteride, a 5-ARIs approved for BPH treatment. Only patients who underwent TURB for the first time with diagnosis of Urothelial Bladder Cancer (UBC) were considered. They were divided in two groups: Group A, (165 patients) including patients that had taken dutasteride 0.5 mg, one capsule daily for at least 1 year before TURB; Group B, (147 patients) including patients untreated with 5-ARIs. The first risk factor for urothelial bladder cancer, namely smoking habits, was found to be not statistically significant between the two groups. The patients were categorized on tobacco-use: never smokers (106; defined as smoking 0–100 cigarettes in their lifetime), smokers (109; smoked more than 100 cigarettes) and former smokers (97; smoked more than 100 cigarettes but had quit smoking before the time of recruitment). The following parameters for UBC were considered: age and number of lesions at first diagnosis, number of lesions in recurrence, number of recurrences and histopathological findings at first resection and in recurrence (Table 1). All surgical specimens were staged according to the TNM classification of the Union Internationale Contre le Cancer (UICC), updated in 2009 [17]; tumour grading was evaluated according to the 2004 World Health Organization (WHO) classification for UBC [18]. All procedures were performed by 3 experienced urologists under spinal/general anaesthesia using a Bipolar Technique with Olympus device and with 0.9% saline as irrigation fluid. The surgical technique and antimicrobial prophylaxis regimens were left to each surgeon's preference. After the procedure, continuous bladder irrigation was initiated until achieving clear urine output and then discontinued. After the surgical procedures (TURB), adjuvant intravesical Mitomycin C (MMC) or Bacillus Calmette-Guérin (BCG) was administered to

all patients, following European Association of Urology (EAU) guidelines [18]. The initial instillation generally occurred within 2–4 weeks of the diagnostic TURB and was repeated once weekly for 6 weeks and once monthly for 6 months. No patient received neo-adjuvant therapy, adjuvant systemic chemotherapy, or radiotherapy. The follow-up of the patients, as recommended by EAU guidelines, consisted of urinary cytology, upper urinary tract ultrasound, or computed tomography urography for the first year, and cystoscopy every three months [18]. Patient therapy was evaluated at each medical examination recorded during follow-up, with particular attention to the use of 5-ARIs.

STATISTICAL ANALYSIS

The statistical analyses were performed using JMP11 software (SAS Institute, Cary, NC, USA) and SPSS software (version 21.0; SPSS Inc., Chicago, IL). Uni- and multivariate modelling was performed with Fine and Gray subdistribution hazards model. The variables were further analyzed in multivariate competing-risk regression models. Subgroup analyses were exploratory, and no adjustments for multiplicity were made. Subdistribution hazard ratios (SHRs) estimated model were reported as relative risks with corresponding 95% confidence intervals (CI). Student t-test for paired samples and ANOVA test were performed to compare the results in the same TURB group and to compare the results between the non-treated and treated with 5-ARIs groups, respectively. The Kaplan-Meier was used to obtain the curve for recurrence-free survival (RFS). P values < 0.05 were considered statistically significant.

RESULTS

In this study, as shown in Table 1, we enrolled a total of 312 male patients divided into two study groups: Group A, (165 patients) represented by the patients treated with dutasteride 0.5 mg and group B, (147 patients) untreated with 5-ARIs. The mean follow-up of group A and group B was 31.37 months (SD: 9.22) vs 29.5 months (SD: 9.7; p value: 0.15), respectively. Both were statistically homogeneous and comparable regarding age, smoking habits and medication history (p value > 0.05). The most represented drug, besides Dutasteride, was cardioaspirin but without statistically significant differences between the two groups. Patients mean age at first diagnosis of bladder tumour in group A and group B was 75.23 years (SD: 10.51) and 75.12 (SD: 9.27, p value: 0.93), respectively

(Table 1). At the time of first resection, between group A and group B, the variables evaluated showed: mean number of bladder lesions 1.7 (SD: 1.44) vs 1.92 (SD: 1.68; p value: 0.323); T-category: pTa 40% vs 35% - pT1 52.2% vs 53.7% - pT2 6% vs 9% - pT3 1.8% vs 2.3% (p values > 0.05); tumour grade: Low Grade 34% vs 24.8%; High Grade 66% vs 75.2% (p values > 0.05); presence of CIS was comparable between the two groups (8.7% vs 10.3%; p value: 0.083), respectively. Clinical and pathological characteristics are shown in Table 1 and Figure 1. All the patients had undergone bladder instillation with intravesical MMC (129) or BCG (153) in accordance with the EAU guidelines without significant difference of distribution between the two groups. During follow-up, 77 patients, 23 (14%) from group A and 54 (37%) from group B (p value: 0.003), showed at least one recurrence of bladder tumour. About relapsing patients, 10 and 13 patients in group A had undergone MMC and BCG respectively (p value > 0.05). The same non statistically significant results were obtained in group B with 24 patients treated with MMC and 30 patients with BCG (p value > 0.05) (Table 1). In particular, recurrent bladder cancer occurred 1.23 times in group A (SD: 0.21) and 1.94 times in group B (SD: 0.14; p value: 0.006) (Table 1, 2, Figure 2). Of these patients, in group A and in group B we recorded T category and tumour grade, respectively: pTa 35.3% vs 33.3% (p value: 0.072); pT1 57% vs 50% (p value: 0.64); pT2 7.7% vs 16.7% (p value: 0.041); low grade: 47% vs 35% (p value: 0.043); high grade: 53% vs 65% (p value: 0.039) (Table 1, Figure 2). The number of tumour lesions between groups A and B at second TURB was not significantly different (mean: 1.13 vs 1.3; SD: 1.3 vs 1.49; p value: 0.750). The relation of these variables and the risk of recurrence regardeing the treatment with 5-ARIs in both groups was confermed in the univariate and multivariate analysis (Table 2). The recurrence-free survival rate of patients treated with 5-ARIs, obtained with Kaplan-Meier curve, was significantly higher compared to patients of group B (SD: 1.07; p value: 0.0001 - log rank test) (Figure 3). In accordance with the EAU guidelines, radical cystectomy was performed on 13 patients from group A (7.8%; SD: 0.27) and 26 patients from group B (17.5%; SD: 0.38; p value: 0.032) (Table 1).

DISCUSSION

There are few studies in the literature concerning the effects of the 5-ARI use in urinary bladder urothelial cancer. This tumour is also known to be more common in men than in women, but the reasons are still relatively unknown [1, 19]. The rationale behind this study is that androgens, as shown in the literature, could play an important role in regulating the

urinary bladder urothelial carcinogenesis, which could explain its higher incidence in male patients [20, 21]. To enhance this hypothesis, previously reported epidemiologic studies have shown an increased risk of bladder urothelial cancer in postmenopausal compared to premenopausal women [22]. Despite the small number of studies related to this possible correlation, it seems that there is a potential role of androgens in urothelial bladder cancer. Few previous studies have reported androgen receptor (AR) expression in urinary bladder tumour and all demonstrated AR immunoreactivity in carcinoma cells [20, 21, 23 – 31]. Moreover, results obtained from experimental studies on animal models suggest the possible stimulatory role of AR mediated intracellular signalling in the development of urinary bladder carcinoma [32].

In literature, there are a growing number of studies that describe the possible correlation between 5a-reductase and urothelial cancer.

A reduced bladder cancer incidence among men taking finasteride, was recently reported in the PLCO study [15]. In line with this notion, our study confirmed the possible role of 5-ARIs, in particular of dutasteride 0.5 mg, that seem to play a prophylactic role in bladder cancer recurrence. Despite the relatively small sample size of our study, we found a significantly lower number of patients with recurrent bladder disease and a lower median number of bladder lesions at recurrence in our statistically comparable groups. Although a low statistical significance, our data would seem to indicate a possible protective role in differentiation of the tumour cells, showing a significantly greater number of low tumour grade compared to high grade in patients treated with dutasteride. We also observed a significant decrease in the number of muscle invasive tumours and therefore of radical cystectomies in patients treated with dutasteride.

Furthermore, a significant improvement in the recurrence-free survival between the first TURB and the recurrence was reported, suggesting that 5-ARIs might be really involved in carcinogenesis. These results again are in agreement with data reported in literature [33], that supposed the role of AR signalling to promote DNA breaks and chromosomal rearrangements, leading to the emergence of oncogenic fusion-genes [34, 35]. Along with the involvement of this pathway to a suppression of detoxification through the control of UDP-glucuronosyltransferases [36], AR signalling seems to promote *de novo* carcinogenesis and bladder cancer recurrence.

As reported in other studies, AR regulates urothelial cell proliferation and the inhibition of this pathway, also with 5-ARIs, has been shown to prevent bladder carcinogenesis and tumour cell proliferation [32, 37]. The involvement of the AR signalling in this kind of

tumour seems to be confirmed by reports of reduced risk of secondary bladder cancer and of the intravesical recurrence in patients with prostate cancer and concomitant NMIBC [14, 16]. In addition, several studies suggest a possible role for AR signalling in migration, invasion, and metastasis of bladder cancer [28, 38].

This study has several limitations such as the relatively non homogeneous small sample size, the absence of female population, and the relatively short follow-up. However, it represents one of the few studies in the literature that analyses and confirms the role of 5-ARIs in a widespread disease such as bladder urothelial cancer. In the future, more studies will be needed related to the molecular aspects involved in the AR pathways because it could open new frontiers in the prevention and treatment of bladder urothelial cancer.

CONCLUSIONS

This study showed a prophylactic role for 5-ARIs in bladder cancer recurrence, in particular of dutasteride 0.5 mg. The group treated with 5-ARIs had a significantly decreased risk of recurrence, a significant improvement of the recurrence-free survival, and fewer numbers of muscle invasive tumours. These encouraging results need to be confirmed by a prospective, randomised controlled study.

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Figure Legends

Figure 1: Pathological data (tumour staging and grading) of patients groups at 1st TURB

Figure 2: Pathological data (tumour staging and grading) of patients groups at recurrence time, men number of relapsing patients and recurrences

Figure 3: The Kaplan-Meier curves of recurrence-free survival rates of patients treated and untreated with 5-ARIs

	GROUP A	GROUP B	P VALUE
No. of patients	165	147	
Mean age, years (SD)	75.23 (10.51)	75.12 (9.27)	0.93
Smoking status, no. (%)			
Never	59 (36)	47 (32)	
Former	53 (32)	44 (30)	≥ 0.05
Current	53 (32)	56 (38)	
Follow-Up, months (SD)	31.37 (9.22)	29.5 (9.7)	0.15
At 1st TURB			
Mean n. of lesions at 1st TURB (SD)	1.7 (1.44)	1.92 (1.68)	0.323
T stage no. (%)			
Pta	66 (40)	51 (35)	
Pt1	86 (52.2)	79 (53.7)	≥ 0.05
≥ Pt2	13 (7.8)	17 (11.3)	
Grade, n. (%)			
Low	56 (34)	36 (24.8)	≥ 0.05
High	109 (66)	111 (75.2)	
Carcinoma in situ, no. (%)	14 (8.7)	15 (10.3)	0.083
Relapsing patients, no. (%)	23 (14)	54 (37)	0.003
Mean no. of recurrences (SD)	1.23 (0.21)	1.94 (0.14)	0.006
Mean no. of lesions at recurrence (SD)	1.13 (1.3)	1.3 (1.49)	0.750
T stage, no. (%)			
Pta	8 (35.3)	18 (33.3)	0.072
Pt1	13 (57)	27 (50)	0.64
≥ Pt2	2 (7.7)	9 (16.7)	0.041
Grade, no. (%)			
Low	11 (47)	19 (35)	0.043
High	12 (53)	35 (65)	0.039
no. of radical cystectomy (%)	13 (7.8)	26 (17.5)	0.032

Table 1. Clinical and pathological patients' characteristics

Table 2: Univariate and multivariate analysis about risk of bladder cancer recurrence related to 5ARIs treatment.

	UNIVARIATE ANALYSIS		MULTIVARIATE ANALYSIS	
	SHR (95% CI)	**p value**	**SHR (95% CI)**	**p value**
Treatment with 5ARIs (yes – no)	0.64 (0.58 – 0.87)	0.006	0.67 (0.52 – 0.85)	0.009
Mean age, years	0.98 (0.78 – 1.14)	0.072	0.89 (0.67 – 1.03)	0.122
Smoking status (Never, Former, Current)	0.87 (0.64 – 1.04)	0.068	0.74 (0.51 – 1.07)	0.268
At 1st TURB				
Mean n. of lesions at 1st TURB	1.07 (0.84 – 1.24)	0.082	1.18 (0.78 – 1.31)	0.133
T stage (pTa, pT1, ≥ Pt2)	0.96 (0.77 – 1.14)	0.062	0.76 (0.58 – 1.11)	0.117
Grade, (Low, High)	0.82 (0.63 – 0.99)	0.102	0.79 (0.61 – 1.03)	0.243
Carcinoma in situ (yes – no)	0.73 (0.53 – 1.09)	0.334	0.75 (0.43 – 1.16)	0.392
MMC	0.92 (0.77 – 1.11)	0.207	1.02 (0.72 – 1.23)	0.315
BCG	0.78 (0.61 – 0.89)	0.076	0.63 (0.41 – 0.97)	0.184

SHR: subdistribution hazard ratio; CI: confidence interval; MMC: Mitomycine C; BCG: Bacillus Calmette-Guérin.