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The Impact of 5-Alpha Reductase Inhibitor vs. Alpha-1 Adrenergic Receptor Antagonists on Course of Prostate Premalignant Conditions

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article; **G** – other

Abstract

Background. Prostate intraepithelial neoplasm and atypical small acinar proliferation are considered prostate premalignant conditions. Such a diagnosis impacts further follow-up significantly as early detection of prostate cancer is of utmost importance. Alpha-1 adrenergic receptor antagonists (i.e. doxazosiunum) and inhibitors of 5-alpha reductase (Finasteride) showed some efficacy in prevention of prostate cancer development.
Objectives. To assess the impact of both abovementioned drugs on prostate premalignant conditions.
Material and Methods. From January 2008 till September 2012, 213 patients with one of the abovementioned premalignant condition were retrospectively evaluated. After diagnosis they were assigned to group 1 (n-126)– treated with Finasteride or to group 2 (n-87)-treated with Doxazosinum. Every 6–7 months rebiopsies were conducted in each patient. Rate of remission and progression was assessed.
Results. In comparison between group 1 and 2 the rate of remission was 35.7% (n-45) vs. 18.4% (n-16) ($p = 0.005$). In terms of progression, the difference between 1st and 2nd group of patients was 7.1% (n-9) vs. 5.7% (n-5) ($p = 0.68$).
Conclusions. Remission of prostate premalignant condition is efficacious with Finasteride and not with Doxazosinum. However, in terms of progression there were no differences among both drugs (**Adv Clin Exp Med 2014, 23, 1, 79–84**).

Key words: prostate cancer, prostate intraepithelial neoplasia, atypical small acinar proliferation, chemoprevention.

Detection of prostate intraepithelial neoplasia (PIN) has recently increased along with the number of biopsies conducted in patients with the suspicion of prostate cancer (Pca). Atypical small acinar proliferation (ASAP) is slightly less frequently diagnosed. Both kinds of dysplasia will treated in a not very distant perspective as strong invasive precursors of Pca [1].

The occurrence of both pathological prostate states is estimated in first biopsy for 4–16% according to high grade PIN (HG PIN) and 3–23% according to ASAP. Rebiopsies obtain respectively 23–47% and 25–57% diagnoses of prostate cancer. The probability of such diagnosis rises with the increased concentration of PSA in serum [2]. In young men, low grade PIN (LG PIN) is most commonly diagnosed. Such lesions are connected with the progression to Pca in patients with PSA serum concentration over 10 ng/mL. There are only a few long-term observations which clearly confirm the high risk of carcinogenesis in patients with LG PIN [3]. Still, only a few authors show similar percentage of Pca diagnosis in rebiopsy independently of the initial diagnosis (LG PIN or HG PIN); i.e. Goeman obtained 27% vs. 30% Pca in rebiopsy, respectively [4].

Many authors have proved in their studies that there is some similarity between HG PIN and Pca in localization in prostate, behavior of potential biomarkers and epidemiology [2].

In a pathological sense, PIN has clearly defined morphological repetitive features [2, 5]. ASAP is an advanced atypia, often doubtfully accompanied by the basal cells damage both focally and multifocally. Due to this fact, it is often not defined histologically in a biopsy specimen, also because of the high percentage of uniqueness of that diagnosis. It is rather a diagnostic category of scheduling the prostate's basal cells with a different grade of probable transformation to Pca [5]. However, at the time of such a diagnosis there are no features of Pca. Therefore, very often immunohistochemical investigations are very helpful in differentiating these two conditions. They reveal uninterrupted basal cells layer of the prostate. It is also speculated that PSA rise is a strong predictor of progression in PIN HG and not in ASAP [6].

The existence of a discrepancy of given morphological images and interpretations in different pathological schools certainly might be an explanation for such situation [7].

The increasingly young age of patients and consequently long period of carcinogenesis to the clinical figure of Pca make these patients perfect candidates for primary prevention and, above all, chemoprevention [8]. Regardless, prostate premalignant conditions (PPC) might be considered markers of the efficacy of the drugs implemented during chemoprevention [2, 9].

It should not be omitted that Pca and PPC might occur in one prostate competitively, next to each other in 6–30% [10].

It is highly possible that these drugs, efficacious in primary chemoprevention, will be effective also in stabilizing the existing cancer during secondary chemoprevention [11]. Both 5-alpha reductase inhibitor (Finasteride) and the antagonists of alpha-1 adrenergic receptor (i.e. Doxazosinum) are the most frequently used medicines against symptomatic dysuria in patients with benign prostatic hyperplasia. This study aims at a comparative analysis of PPC chemoprevention using the abovementioned medicines with simultaneous evaluation of subjective improvement of lower urinary tract symptoms (LUTS). In addition, the meaning of predictive factors of the risk of Pca development such as prostate volume, total serum PSA (T PSA) and total testosterone (TT) concentration and the influence of chemoprevention on their behavior were defined.

Material and Methods

The study was conducted from January 2008 till September 2012. The analysis covers 213 men in whose histopathological examination after the transrectal biopsy (TRU CUT) revealed one of the above PPC. Patients with PSA T concentration higher than 4 ng/mL or/and pathology in digital rectal examination were qualified for biopsies.

The first biopsy was usually sextant. During rebiopsy done 6–7 months after the first one, 12 cores were collected. Before each biopsy, the PSA T (electrochemiluminescence method ECLIA) and TT concentration (electrochemiluminescence method ECLIA in Elecsys 2010 analyzer) were analyzed as well as the prostate volume (after evaluating 3 prostate diameters) using the formula width × height × length × 0.52. The dysuria was evaluated in IPSS scale (0–35points) where the standard is located between 0–7 points, with simultaneous quality of life evaluation (QL) in 6-grade scale with the normal range between 0–2 points. Patients filled out the survey on their own. For PSA T concentration – 4 ng/mL and for TT concentration – 3.4 ng/mL were considered standard. Measurements were made in the morning (9:00––10:00 AM). Patients were divided into 2 groups. The first group (n-126) consisted of patients taking Finasteride in 5 mg dose a day, while the second one (n-87) – Doxazosinum (Doxar®) in 4 mg dose a day. All mentioned treatments and diagnostics were repeated every 6–7 months. Histopathological examination was done by two independent uropathologists. Lack of any of the PPC changes described above was considered a criterion of remission. Progression was diagnosed in patients at the moment of morphological Pca confirmation present in prostate's core biopsy. Statistical software v. 8 (StatSoft, Tulsa, OK, USA) was used in statistical evaluation. All statistical tests were two-sided with $p < 0.05$ considered to be statistically significant. The check for normality of the variables' distribution were done using the Shapiro-Wilk test. For dependent samples without standard parametric distribution Wilcoxon matched pairs was applied. For categorical variables Chi Square test was used. In distributions which were different from the standard – the *U*-Mann-Whitney test was used. Correlations between variables were evaluated and presented with *R* Spearman correlation coefficient.

Results

Among 213 patients who underwent the treatment in 148 – LG PIN was diagnosed, in 46 – HG PIN and in 19 – ASAP. The duration of medical treatment ranged from 7 to 33 months (18.7 on average). Patients were 47–79 (67.3 on average) years of age. The initial PSA T concentration was averagely 7.9 ng/mL (range: 1.9 – 24.2 ng/mL), while

an average TT concentration was 4.3ng/dL (range: 2.9 – 7.6 ng/dL). An average prostate volume was 36.4 cm3 (range: 29.3 – 46.7). The IPSS ranged from 7–22 points, averagely 13 pts. The remission of PPC was diagnosed in 61 patients (28.6%). In the 1st group remission was observed in 44.4% of patients suffering from LG PIN, and in 27.3% suffering from HG PIN and in 0% suffering from ASAP. The 2nd group showed the following results – 19.4%, 23.1%, and 0%, respectively.

In comparison between group 1 and 2 the rate of remission was 35.7% vs. 18.4% with a difference of 17.3% (p = 0.005) (Table 1). Between patients with LG PIN in 1st vs 2nd group, there were also statistically significant differences in terms of remission. However, in the case of HG PIN and ASAP there was no statistical significance.

The progression of PPC has been found in 14 patients (6.6%). In the 1st group of patients it was 0% in LG PIN, 15.1% in HG PIN and 33.3% in ASAP. In the 2nd group – 1.5%, 15.4% and 28.6%, respectively. Altogether the difference between 1st and 2nd group of patients was 7.1% vs. 5.7% and equaled 1.4% (p = 0.68). A different situation occurs in patients with remission. There are no statistical differences in progression between the groups and kinds of PPC (Table 2).

In both groups of patients the remission of PPC was accompanied by an increase in TT concentration which only in group 2 appeared to be statistically significant (p = 0.0157). In *U*-Mann-Whitney test, the initial TT concentration in patients with remission was higher in relation to the rest (p = 0.0285). Still, it did not correlate with the increase in PSA T concentration or prostate volume (r = 0.45, p = 0.68; r = 0.48, p = 0.82 respectively). The PSA T concentration in patients with remission was insignificantly lower in relation to the patients with progression (p = 0.0685). On the other hand, statistical significance was observed in an analysis of PSA T in group 1 between patients with remission and progression (p = 0.0033).

Among 14 patients with progression, in 5 (35.7%) the tumor grade in Gleason score was higher than 7, in 2 patients it equaled 7 (14.3%) and in the rest (50%) it was lower than 7. In group 1, it was on average 6.9 vs. 6.6 in the second group (p = 0.810). In the 1st group of patients with remission, statistically a significant decrease in prostate volume was noticed (12.2%, p = 0.0076**).** In the 1st group, prostate volume was correlated with the decrease of PSA T concentration (r = 0.74, p = 0.03). In the first group, in patients with progression, the decrease in prostate volume was noticed (p = 0.0328)

Table 1. The influence of chemoprevention on PPC remission rate

Type of PPC	Group I		Group II		p value
	No. of patients	No. of patients with remission (%)	No. of patients	No. of patients with remission (%)	
LG PIN	81	36 (44.4)	67	13 (19.4)	0.001
HG PIN	33	9 (27.3)	13	3 (23.1)	0.77
ASAP	12	0	7	0	Ns
All	126	45 (35.7)	87	16 (18.4)	0.005

PPC- prostate premalignant condition; LG PIN – low grade prostate intraepithelial neoplasia; HG PIN – high grade prostate intraepithelial neoplasia; ASAP – atypical small acinar proliferation.

Table 2. The influence of chemoprevention on PPC progression rate

Type of PPC	Group I		Group II		p value
	No. of patients	No. of patients with progression (%)	No. of patients	No. of patients with progression (%)	
LG PIN	81	0	67	1 (1.5)	0.26
HG PIN	33	5 (15.1)	13	2 (15.4)	0.98
ASAP	12	4 (33.3)	7	2 (28.6)	0.82
All	126	9 (7.1)	87	5 (5.7)	0.68

PPC – prostate premalignant condition; LG PIN – low grade prostate intraepitheliual neoplasia; HG PIN – high grade prostate intraepithelial neoplasia; ASAP – atypical small acinar proliferation.

but without a strong correlation with PSA T and TT. In patients with remission, the difference between 1 and 2 group (IPSS scale) after chemotherapy equaled 3.3 pts and was statistically significant ($p = 0.0244$). Overall, between patients with remission vs. progression, the difference equaled 1.2 pts and did not have the features of statistical significance ($p = 0.5$). Along with the IPSS survey, the QL was evaluated and showed insignificant statistical improvement in patients with remission vs. progression ($p = 0.124$).

Discussion

Currently, we are not using any specific biomarker or other diagnostic methods that would allow us to evaluate the risk of Pca development in men with PIN and ASAP. In case of both kinds of prostate dysplasia, the indicators of aneuploidy and angiogenesis are similarly increased. The index of proliferation and apoptosis are also similar [5]. This considerable similarity to the changes noticed in patients with Pca causes the prostate biopsy to be the diagnostically conclusive test [1, 12]. In practice, we often face the problem when the suggested chemotherapy influences the risk of carcinogenesis. It is quite understandable that not only the kind of chemotherapeutics and its duration, but also the current hormonal status of the patient (i.e. hypogonadism), his lifestyle and diet influence the result [8, 13]. The lack of clearly established facts as far as this issue is concerned is strange because the scale of this phenomenon is becoming wider and rises with the improvement of diagnostics in patients with Pca suspicion. In the USA, about 115 thousand patients with HG PIN are recognized – 9% of all biopsies, 3–5% with ASAP and many more have to be added to this number (approximately 12–14% with LG PIN) [14]. According to the opinion shared by majority of the authors, Pca will be diagnosed in 1 per 7 men throughout his life. Considering that in most cases, it will be a clinically insignificant cancer, still it remains a significant problem, not only medical but also socio-economic. An active primary chemoprevention seems to be a logical answer to this challenge [9].

The aim of this study was to evaluate the influence of the most frequently used drugs during LUTS therapy in patients with high risk of Pca progression. The thesis that allows implementing antagonists alpha-1 adrenergic receptor, particularly those with quinazolin ring (Doxazosinum and Terazosinum) holds that it has an inhibitory effect on Pca cells [15]. Nowadays, it is believed that one of the mechanisms might be an intermediate influence on the apoptosis of cancers cells. Another postulated mechanism is that these medicines work as angiogenesis inhibitors. In recent years, the PTEN inactivation and Bcl-2 degradation are the most widely described potential mechanisms that justify their effects in chemoprevention [16]. The most possible mechanism of Doxazosinum is to induce apoptosis through Akt induction [17]. Despite a quite broad theoretical basis, clinical studies do not confirm the efficacy of this group of medicines in Pca chemoprevention, both as primary and as secondary ones [18]. Retrospective analysis of over 2,000 patients taking Doxazosinum in arterial hypertension showed a decrease in the percentage of patients suffering from Pca by 40% compared to the control group. Still, Harris's report is a very sparse exception [16]. In turn, almost 4,000 patients taking alpha-adrenolytics during European Randomized Study of Prostate Cancer Screening Trial by Finnish authors, proved no influence of these medicines on the incidence of prostate cancer. The significant part of this case study was an allegation concerning the decrease in percentage of high grade malignant Pca.

In relation to 5-alpha reductase inhibitors, their efficacy in Pca prevention was repeatedly confirmed, and it also refers to PPC [19, 20]. Theoretical basis that allows for the implementation of this group of medicine in primary and secondary chemoprevention is connected to its influence on the alternative signal transduction pathways in prostate cells for adrenergic receptor [11].

In light of the gained results, there is no significant difference in the percentage of progression in patients treated with Doxazosinum vs Finasteride ($p = 0.68$). Such a difference is visible in patients with remission ($p = 0.005$). It seems that we also cannot confirm the observation of the authors describing the decrease in highly malignant prostate cancers after Doxazosinum [16] or an increase in their percentage after Finasteride [21]. In relation to Doxazosinum, the remission's results might prove that the positive influence on PIN, especially in relation to HG PIN. If, as claim Bono et al., the HG PIN remission might also exist independently (without treatment) in as many as 13% of patients, the positive influence would be objectively visible (27.3%) but moderate [22]. For Finasteride, the results seem to confirm the data from PPC meta-analysis, where the decrease in percentage of HG PIN by 21% was shown [21]. This test, as well as the studies conducted by other authors, confirms the increase of highly malignant forms obtained in rebiopsies [18]. Finasteride's influence on remission is statistically significant but is only limited to PINs, especially to LG PIN. In patients with ASAP, the lack of remission and presence of progression

is significantly higher in both groups than in patients with PIN. These observations are consistent with outcomes presented by other authors [6, 14]. Braussi et al. conducted radical prostatectomy in 30 patients with pathologically confirmed diagnosis of ASAP. In postoperative examination, they obtained in all patients a histological confirmation of Pca [23]. On such a basis, he presents the thesis that the radical treatment of ASAP is not considered as overtreatment. The absence of remission as well as the high percentage of progression in patients with ASAP confirms such a thesis on the basis of our observations.

Shandu et al. claim that the Pca volume and HG PIN correlate with prostate size. Therefore, a small prostate volume is a predictor of invasive Pca. The Pca tumor's volume is inversely proportional to prostate volume, which directly influences PSA T concentration. It could not be confirmed in the case of PIN or ASAP in our study. The authors explain this by saying that 1g Pca causes an increase in PSA T on an average by 0.8 ng/mL, while 1g of non-tumor tissue only by 0.07 ng/mL. (11 times less) [7, 24]. The decrease in prostate volume after chemoprevention should improve the LUTS parameters in patients from group 1 in terms of both remission and progression, but there is no correlation between those results ($r = 0.44$, $p = 0.682$). The expected IPSS scale improvement occurred in the second group of patients with remission, but also not connected with the decrease in prostate volume. That change has only correlated with the increase in TT concentration ($r = 0.67$, $p = 0.0338$).

Currently, there is no unequivocal evaluation of typical mutual behavior between PSA T concentration and increase in TT concentration in patients with PPC [13]. As far as the opinions on the influence of low TT concentration on the frequency of PPC and Pca are divided, the majority of authors believe that they are accompanied by higher malignancy grade. It expresses itself through higher grade in Gleason score as well as the higher percentage of locally advanced forms of Pca [25]. An increase in TT concentration (often also with PSA T concentration) is accompanied by an increase in Pca diagnosis, so its increase in patients with PPC is to be proof of progression [26]. We did not observe such dependence among treated patients. Similarly, the increase in TT concentration was not accompanied by a significant increase in PSA T concentration. It is possible that an almost 19-month period (on average) of observation is not enough to reveal the discussed dependence, as well as an insufficient number of patients did not allow for an evaluation of statistically strong connections between considered factors. Part of these concerns might have been answered by adding and assessing a placebo group [22]. However, in the experimental environment, this is hard to conduct not only due to ethical concerns. Still, part of the results are understandable and result from e.g. low initial scoring in relation to IPSS [10 pts] and QL [2.6 pts]. The prostate was also, initially, not too big [36 cm^3]. There was no increase in prostate volume with the simultaneous lack of the TT and PSAT concentration during the Finasteride therapy does not exclude progression to Pca. Similarly, there was no increase in prostate volume with a decrease of PSA T and an increase in TT may indicate remission. That is why the changes did not manage to reveal themselves. The only sure statement resulting from our work is the absence of remission in the treated patients with ASAP and a high risk of progression, regardless of the implemented chemotherapeutics. Due to the isolated character of the clinical and laboratory changes and the lack of significant correlation between them, it has to be ascertained that rebiopsy every 6–7 months should be an obligatory procedure in PPC. Patients with ASAP should receive special observation and controlled supervision.

Authors concluded that after Finasteride chemoprevention, the remission of PPC is significantly more frequent than after Doxazosinum chemoprevention, but only in relation to LG PIN it is a statistically significant difference.

After 19 months of chemoprevention, there were no significant differences in the percentage of progression between compared therapeutic groups.

An increase in TT concentration promotes remission in patients treated with Doxazosinum.

A decrease in prostate volume with the lack of the TT and PSA T concentration growth during the Finasteride therapy does not exclude progression to Pca. Similarly, a decrease in prostate volume with decrease of PSA T and an increase in TT may indicate remission.

The diagnosis of PPC in first biopsy should always indicate the need for rebiopsy.

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