Role of 5α-Reductase Inhibitors in Prostate Cancer Prevention and Treatment

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Although testosterone is the most abundant serum androgen, dihydrotestosterone is the main prostatic androgen. Testosterone is converted to dihydrotestosterone by the enzyme 5α-reductase (5α-R). Dihydrotestosterone plays an important role in several human diseases, including benign prostate enlargement and prostate cancer. The observation that males born with 5α-R 2 deficiency have never been reported to develop prostate cancer stimulated interest in development of 5α-R inhibitors. Thus far, 2 5α-R inhibitors are approved for clinical use. Several trials evaluated the use of 5α-R inhibitors in prostate cancer prevention and treatment and will be reviewed in this article. UROLOGY 79: 1197–1205, 2012. © 2012 Elsevier Inc.

Although testosterone (T) is the most abundant serum androgen, dihydrotestosterone (DHT) is the main prostatic androgen. DHT has 2-5 times higher binding affinity for the androgen receptor (AR) than T, and 10-fold higher potency of inducing AR signaling than T. T is converted to DHT by the enzyme 5α-reductase (5α-R).

DHT plays an important role in several human diseases, including benign prostatic enlargement (BPE) and prostate cancer (CaP). The role of DHT was recognized after discovery in 1974 of 5α-R2 deficiency. Affected males are born with normal internal but ambiguous external genitalia. Their prostates are hypoplastic, nonpalpable on examination, and comprised of fibromuscular tissue, with no identifiable epithelium. Neither BPE nor CaP has been reported in these patients.

Three 5α-R isozymes have been discovered and are ubiquitously expressed in humans.[1] 5α-R1 and 5α-R2 are the most well studied and are involved mainly in steroid 5α-reduction. 5α-R3 is important for N-glycosylation of nascent proteins.[2] Types 1 and 3 are upregulated in primary and castration-recurrent (CR) CaP compared with benign prostatic tissue.[3-5] Furthermore, types 1 and 2 are upregulated in high Gleason vs low Gleason score (GS) CaP and also in CR–CaP and metastatic CaP vs prostate intraepithelial neoplasia (PIN).[4,5] Interest in development of 5α-R inhibitors (5α-RI) started after discovering the implications of 5α-R2 deficiency. Numerous compounds were developed but only 2 drugs were FDA approved for clinical use. Finasteride was approved for treatment of BPE and male alopecia, and dutasteride was approved for BPE treatment.

CaP is the most common noncutaneous malignancy and the second most common cause of cancer death in American men. The risk of CaP increases with age and more men are expected to be diagnosed with CaP every year, given increasing average life expectancy. CaP has low mortality because 5 of every 6 American men with CaP die of other causes. Treatment options are associated with significant morbidity and are administered unnecessarily in 40-50% of men with clinically localized disease.[6] CaP is a significant public health problem and an ideal target for prevention.

Chemoprevention is defined as the use of specific natural (dietary) or synthetic agents to prevent, delay, or slow carcinogenesis. Primary chemoprevention refers to reducing the risk of cancer development, eg, avoidance of environmental pollutants and use of sunscreens. Secondary chemoprevention includes detection of cancer at an early stage when still asymptomatic and the chance of cure is very high (ie, screening), and reducing the risk of progression of an existing cancer. Because autopsy studies found that as many as 30% of men in their 30s have foci of CaP and prevalence increases nearly 10% per decade[7]; CaP prevention should involve both primary and secondary chemoprevention.

Nearly 30% of CaP patients who receive local therapy with curative intent fail biochemically. Without salvage treatment, two-thirds will develop clinically evident bone metastasis after 10 years and will eventually die of CaP.[8] Androgen deprivation therapy (ADT) is the standard treatment for metastatic disease; however, it is not curative and is associated with significant adverse effects (AEs).

5α-R inhibition is a rational method of CaP prevention and treatment. CaP is androgen-stimulated and DHT is the main prostatic androgen. 5α-R isozymes are upregulated in CaP. CaP has not been reported in eunuchs or males with 5α-R2 deficiency. Furthermore,

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5α-R inhibition is a mild form of androgen manipulation that interferes with the production of DHT without depriving the body of T 5α-R inhibition potentially spares patients many of the AEs associated with ADT. Several trials evaluated the use of 5α-RI in CaP prevention and treatment, and will be reviewed in this article.

PREVENTION OF CaP

Table 1 compares the Prostate Cancer Prevention Trial (PCPT) and the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial.[9,10] Both trials had different designs and patient populations, which make their conclusions complementary. PCPT was the first large-scale primary chemoprevention trial against CaP. At the study's end, 9060 participants (48% of randomized men) were evaluable for the primary endpoint. For-cause biopsies were done in 39% of the participants and 51% of CaP was diagnosed in for-cause biopsies. There were fewer for-cause and end-of-study biopsies in the finasteride arm. CaP was diagnosed in 18.4% and in 24.4% in the finasteride and placebo groups, respectively, which represented 24.8% relative risk reduction (RRR) in CaP prevalence. The benefit of finasteride vs placebo in reducing the risk of CaP was apparent across all subgroups studied by age, ethnicity, family history of CaP, and baseline serum prostate-specific antigen (PSA) levels, with hazard ratios between 0.66 and 0.81. The risk reduction in the finasteride arm was seen in clinically apparent (diagnosed by for-cause biopsies) and subclinical tumors (diagnosed by end-of-study biopsies). However, significant increases in the diagnosis of high GS CaP were observed with finasteride vs placebo. Equal numbers of CaP deaths[5] were observed in each arm. Sexual AEs were more common with finasteride, whereas urinary symptoms were more common with placebo ($P < .05$ for both).

The rationale behind using dutasteride in REDUCE was the increased expression of 5α-R1 and 5α-R2 in localized, high-grade CR–CaP and metastatic CaP, as well as the reduced risk of CaP diagnosis by 50% in men with BPE-induced lower urinary tract symptoms (LUTS) treated with dutasteride for 27 months compared with placebo[11] (although this was a post hoc analysis, such decreases were not observed in similarly designed trials with finasteride).[12,13] The primary endpoint was CaP prevalence on protocol-mandated and for-cause prostate biopsies. For-cause biopsies performed during months 19-24 and 43-48 replaced the protocol-mandated year 2 and year 4 biopsies, and hence did not increase a subject's chance of CaP diagnosis. Unlike PCPT, for-cause biopsies were infrequent in REDUCE (5.8% in the dutasteride and 7.7% in the placebo groups). Pathologic assessment used the classic GS system where the most and second-most prevalent architectural patterns occupying >5% of tumor volume were labeled as the primary and secondary Gleason grades.

CaP was diagnosed in 25.1% and 19.9% of men in the placebo and dutasteride groups, respectively (RRR 22.8%). At the study's end, GS 7-10 cancers were diagnosed in 220 (6.7%) and 233 (6.8%) of men in the dutasteride and placebo groups, respectively ($P = .81$). GS 8-10 cancers were diagnosed in 29 (0.9%) men in the dutasteride group and in 19 (0.6%) men in the placebo group ($P = .15$). During the first 2 years, 17 and 18 GS 8-10 cancers were diagnosed in the dutasteride and placebo groups, respectively ($P = 1$). However, during years 3-4, 12 GS 8-10 cancers were found in the dutasteride group and only 1 was found in the placebo group ($P = .003$). To evaluate for potential underestimation of GS 7-10 cancers in REDUCE by use of the classic GS system in the original analysis, the FDA requested an independent, blinded reassessment of grade using the 2005 International Society of Urological Pathology modified GS system (primary and secondary grades are the most prevalent and highest grades, respectively, regardless of volume).[14] Reassessment was consistent with the classic GS (concordance index 0.83), with an overall CaP–RRR of 20.4% for dutasteride using the modified GS. The effects of dutasteride on GS 2-6 cancers were similar using either grading system (RRR 27% [classic] or 26% [modified], $P < .0001$). Dutasteride had no meaningful effect on GS 7-10 cancers using either grading system. More cases of GS 8-10 cancers were diagnosed in the dutasteride arm using either system. Although the difference was statistically insignificant using the classic system ($P = .15$), twice as many cases were diagnosed in the dutasteride arm using the modified system (16 vs 32, $P = .0196$). Trends in GS 8-10 cancers were similar using the 2 grading systems when stratified by years 1-2 vs years 3-4.

Similar to finasteride, the benefit of dutasteride in CaP risk reduction was apparent across all subgroups, including age, family history, and baseline PSA (RRR 22-32%).

Most drug-related AEs were mild or moderate, rarely led to drug discontinuation, and resolved while on therapy in some subjects. The most common AEs were erectile dysfunction, altered libido, ejaculation disorders, and breast enlargement/tenderness, and were reported mainly in the first 6 months of therapy. There was a significant difference in cardiac failure events between the dutasteride (0.7%) and placebo (0.4%) groups ($P = .03$). After careful review of all cardiac failure cases by the manufacturer and the FDA, the FDA concluded that no causal relationship exists between dutasteride and cardiac failure because most cases occurred in subjects with concomitant medical conditions that put them at increased risk for cardiac failure events.[14]

PCPT and REDUCE generated much controversy, regarding the role (if any) of 5α-RI in CaP prevention. Table 2 lists the most important controversial points. In 2009, the American Urological Association and the American Society of Clinical Oncology issued a joint statement that cautiously recommended 5α-RI use for 7 years as an option for primary chemoprevention against CaP but only after thorough discussion of the benefits and risks of these drugs.[37] Candidates for 5α-RI use for

Table 1. Comparison between PCPT and REDUCE

	PCPT	REDUCE
Study design	Prospective randomized, placebo-controlled	Prospective, randomized, placebo-controlled
No. randomized	18,882 men (9423 in F, 9457 in P)	8231 men (4105 in D, 4126 in P)
No. analyzed	9060 (4368 in F, 4692 in P)	6726 (3305 in D, 3424 in P)
Inclusion criteria	Age ≥55 years Normal DRE IPSS score <20 Serum PSA level ≤ 3.0 ng/mL	Age 50-75 years PSA 2.5-10 ng/mL Prostate volume ≤80 cm^3 and a single, negative 6-12 core prostate biopsy within 6 months before enrollment
Excluded	History of HGPIN Prior use of 5α-RI	History of HGPIN Prior use of 5α-RI Prostate size >80 mL
Prostate biopsy	6-core	10-core
PSA correction factor in the 5α-RI group	2 (years 1-3) 2.3 (years 4-7)	2
CaP risk in participants	Low-intermediate	High
Intervention	Finasteride 5 mg/d vs placebo	Dutasteride 0.5 mg/d vs placebo
Length of study	7 y	4 y
Biopsy Gleason scoring system used in original publication	Modified: Primary grade: most prevalent pattern Secondary grade: highest pattern	Classic: Primary grade: most prevalent pattern Secondary grade: 2nd most prevalent pattern
Primary endpoint: Period prevalence of CaP diagnosed by protocol-mandated and for-cause biopsies	All CaP F: 803 of 4368 men (18.4%) P: 1147 of 4692 men (24.4%) RRR: 24.8% (PS) GS 7-10 CaP: F: 280 of 4368 men (6.4%) P: 237 of 4692 men (5.1%) RRI: 25.5% (PS) GS 8-10 CaP: F: 90 of 4368 men (2.1%) P: 53 of 4692 men (1.1%) RRI: 91% (PS)	All CaP: (classic/modified GS) D: 659/3305 men (19.9%) [19.5%] P: 858/3424 men (25.1%) [24.5%] RRR: 22.8% [20.4%] (PS for both) GS 7-10 CaP: (classic/modified GS) D: 220/3305 men (6.7%) [6.3%] P: 233 of 3424 men (6.8%) [6.7%] RRR: 1.5%, [6%] [PNS for both] GS 8-10 CaP: (classic/modified GS) D: 29/3305 men (0.9%) [1%] P: 19/3424 men (0.6%) [0.5%] RRI: 50% [100%] ($P = .15$) [$P = .02$]
Definition of for-cause biopsies	Biopsies performed for abnormal DRE and/or PSA >4 ng/ml (adjusted for effect of F)	Biopsies performed based on physician discretion
Timing of protocol-mandated biopsies	At end of study (7 y ± 90 d)	At 2 and 4 years, including for-cause biopsies performed (19-24 months) and (43-48 months) after randomization
% for-cause biopsies	F: 38% of men P: 39% of men	D: 5.8% of men P: 7.7% of men
% CaP diagnosed on for-cause biopsies	F: 53% of all CaP P: 49% of all CaP	D: 6.2% of all CaP P: 6.6% of all CaP
% CaP diagnosed on protocol-mandated biopsies	56% of all CaP	91% of all CaP
Secondary endpoints	Effect on HGPIN (without CaP): F ↓ HGPIN by 15% BPH outcomes: F ↓ risk of AUR by 33% F ↓ risk of BPE-related surgery by 47% F ↓ risk of UTIs by 29%	Effect on HGPIN (without CaP): D ↓ HGPIN by 43% BPH outcomes: D ↓ risk of AUR by 77% D ↓ risk of BPE-related surgery by 73% D ↓ risk of UTIs by 41%
Most common adverse effects: (PS for all comparisons)	Erectile dysfunction: 67% (F) vs. 62% (P) Decreased libido: 65% (F) vs. 60% (P) Ejaculation disorder: 60% (F) vs. 47% (P) Breast enlargement: 4.5% (F) vs. 2.8% (P) Breast tenderness: 8.8% (F) 6.2% (P)	Erectile dysfunction: 9% (D) vs. 5.7% (P) Decreased libido: 3.3% (D) vs. 1.6% (P) Ejaculation disorder: 1.4% (D) vs. 0.2% (P) Breast enlargement: 2% (D) vs. 1% (P)

f = finasteride; p = placebo; d = dutasteride; DRE = digital rectal examination; IPSS = International Prostate Symptom Score; HGPIN = high-grade prostatic intra-epithelial neoplasia; RRI = relative risk increase; PS = *P* value statistically significant; PNS = *P* value statistically insignificant; AUR = acute urine retention; UTI = urinary tract infection.

Table 2. Pros and cons for 5α-RI use for CaP prevention

Evidence Supporting Use of 5α-RI in CaP Prevention	Evidence Against Use of 5α-RI in CaP Prevention
1. 5α-RIs decrease the diagnosis of overall and low-grade CaP. This should lead to a reduction in the overdiagnosis and overtreatment of indolent CaP. Up to 90% of all CaP undergo an aggressive form of treatment.[15] In REDUCE, dutasteride reduced treatment interventions for CaP by 32%.[16]	1. Only 48% of randomized men were evaluable for the primary endpoint at the end of PCPT.
2. 5α-RIs reduce the incidence of HGPIN, a marker of increased risk of CaP on a subsequent biopsy (by 15% in PCPT and 39% in REDUCE)	2. In both trials, the percent of positive biopsies in the placebo group (25%) exceeded the published lifetime risk of CaP (17%), which suggested that many of tumors were clinically insignificant.[30]
3. Focus should not only be on the for-cause biopsy group, because the design and statistical power of PCPT and REDUCE were intended to see whether 5α-RIs affected the prevalence of biopsy-detectable CaP, more so than clinically apparent tumors.	3. The for-cause biopsy group is the important group to look at because in clinical practice, prostate biopsies are done only for cause. In PCPT, there were 10% fewer cancers diagnosed in the finasteride vs placebo arms (26.5% vs 29.5%; $P > .05$). In REDUCE, of biopsies performed for cause outside the protocol, 16.6% in the dutasteride and 16.7% in the placebo groups were positive ($P > .05$). Thus, neither dutasteride nor finasteride significantly reduced the risk of CaP among men who underwent a biopsy because of an increased suspicion of CaP.[30,31]
4. In REDUCE original publication, there were no significant differences between dutasteride and placebo groups in diagnosis of GS 7-10 and 8-10 CaP.	4. The reduction in overall CaP incidence in PCPT and REDUCE was entirely caused by reduction in GS 2-6 (PCPT) and GS $\leq 3 + 4 = 7$ CaP (REDUCE).
5. 5α-RI enhances the detection of high-grade cancer by improving the performance of PSA and DRE.[17,18]	5. More overall GS ≥ 7 CaP (PCPT) and GS $\geq 4 + 3 = 7$ CaP (REDUCE) were diagnosed in the 5α-RI than the placebo arms.
6. 5α-RI improves the sensitivity of prostate biopsies by reducing prostate volume and making cancers, regardless of their grade, easier to detect.[19,20]	6. More GS 8-10 CaP (overall in PCPT, during years 3-4 in REDUCE) were diagnosed in the 5α-RI than the placebo arms.
7. Secondary analyses suggested that finasteride leads to an earlier detection of high-grade cancer, which would be less extensive at surgery, and that if high-grade cancers were present at RP, they were more likely to be detected in the finasteride than placebo arms.[21]	7. Using the modified GS, more overall GS 8-10 CaP were diagnosed in the dutasteride arm in REDUCE.[14]
8. 5α-RI probably do not induce high-grade CaP. Several secondary analyses concluded that finasteride and dutasteride reduce high-grade CaP. When prostate volume at the time of biopsy was included in a logistic regression model, the odds ratio for GS ≥ 7 in the finasteride arm was 0.88 and in the dutasteride arm was 0.62.[22,23]	8. In both trials, for patients who believe they are taking a drug to prevent CaP, the decline in PSA level can lead to a false sense of security.[30]
9. In a study of men with GS 4-7 CaP on active surveillance, 8% of men were upgraded to GS 8 cancers on re-biopsy performed an average of 22 months later.[24] In REDUCE, there were 141 more GS 5-7 cancers diagnosed in the placebo arm during years 1-2 who were removed from the study and did not receive the second set of biopsies at the end of year 4. Eight percent of those 141 GS 5-7 tumors (11 patients) would be upgraded had they undergone the second biopsy.	9. In both trials, fewer biopsies were performed in the 5α-RI groups.
10. In the CombAT trial (4-year prospective randomized controlled trial of tamsulosin-dutasteride combination vs. either drug alone in men with BPH at increased risk of progression), all biopsies were done for a cause. There was no increase in high-grade cancers in the 2 dutasteride arms compared with the tamsulosin monotherapy arm.[25]	10. The Finnish Prostate Cancer Trial showed decreased incidence of GS ≤ 6 CaP (HR 0.28) and increased incidence of GS ≥ 7 CaP (HR 2.49) among long-term users of finasteride (≥ 1087 doses) compared with men on placebo.[32]
11. The REDEEM trial, which tests the role, if any, for dutasteride in low-risk CaP patients on active surveillance was recently reported.[26] Protocol-mandated biopsies were performed at 18 months and 3 years of treatment. Over 3 years, dutasteride decreased CaP progression (histologic progression or receipt of active treatment) by 39%, increased the percent of men with no cancer on final biopsy (at 36 months) by 57%, and decreased CaP-related anxiety. No increased GS upgrading was reported with dutasteride.	11. All secondary analyses suggesting that 5α-RI do not induce high-grade CaP are retrospective and hypothesis-generating, not confirmatory.
	12. A cost-utility analysis found that 5α-RIs are unlikely to be cost-effective because of the usually indolent natural history of treated CaP. However, these agents may be cost-effective in high-risk groups.[33]
	13. Follow-up in PCPT and REDUCE is short and the effects on CaP-specific and overall survival are unknown.
	14. The CombAT study was not designed to study the effect of BPE treatment on CaP risk.
	15. Sexual AEs are more common in the treatments arms. Even though sexual AEs fade over time, gynecomastia continues steadily at a slow rate in 5α-RI users.[27,28]

Table 2. Continued

Evidence Supporting Use of 5α-RI in CaP prevention	Evidence Against Use of 5α-RI in CaP prevention
12. 5α-RI had beneficial effects on BPE-related clinical outcomes. 13. Both drugs are well-tolerated.[27,28] Rate of sexual AEs is similar to placebo after the first 6-12 months. 14. Studies of 5α-R type 2 gene polymorphisms are inconclusive regarding the relationship between increased or decreased 5α-R type 2 activity and risks of CaP (overall) and high-grade CaP. Evidence exists that increased 5α-R type 2 activity because of A49T substitution is associated with 7.2-fold and 3.6-fold increased risk of Gleason score ≥7 CaP in African-Americans and Hispanics, respectively[29]	16. Studies of 5α-R type 2 gene polymorphisms are inconclusive regarding the relationship between increased or decreased 5α-R type 2 activity and risks of CaP (overall) and high-grade CaP. Decreased 5α-R type 2 activity caused by V89L gene polymorphism is associated with increased risks of overall CaP (by 1.89 folds in LL genotype) and GS >7 CaP (by 2.6-fold in LL genotype).[34] Other studies of V89L polymorphism indicate either the lack of an association[35] or decreased risk of CaP.[36]

ASCO = American Society of Clinical Oncology; HR = hazard ratio.

CaP risk reduction are asymptomatic men and men with BPE-induced LUTS, already on 5α-RI, whose PSA is ≤3.0 ng/mL and are screened regularly for CaP. The statement concluded that 5α-RI clearly reduces the overall risk of CaP and the risk of low-grade disease, and improves BPE endpoints at the expense of a slightly increased risk of high-grade disease and a definitely higher but reversible risk of sexual dysfunction that decreases over time. No specific PSA cut-point could be recommended as a trigger point for prostate biopsy in 5α-RI users. Furthermore, no trial in the literature was large enough or had sufficient long-term follow-up to detect differences in CaP-specific and overall mortality. The statement also recognized that even if CaP risk reduction does not translate to reduced mortality, reductions in CaP diagnosis and associated morbidities (of diagnosis and treatment) are relevant.

In January 2011, the FDA's Oncologic Drug Advisory Committee voted against recommending 5α-RI for CaP risk reduction because of the potential increased risk of high-grade disease.[37] However, this risk—whether real or artifact—is small. In PCPT and REDUCE, the number needed to harm (to cause 1 GS 8-10 CaP) is 100 and 200-333, respectively. In other words, 1 man is diagnosed with GS 8-10 CaP for every 6, and for every 10-17 prevented cases of any GS CaP, in PCPT and REDUCE, respectively (Table 3).

Table 3. Numbers needed to treat and harm in PCPT and REDUCE

	PCPT	REDUCE*
NNT (to prevent 1 case of any GS CaP)	17	19-20
NNH (to cause 1 GS 7-10 CaP)	77	NA
NNT (to prevent 1 case of GS 7-10 CaP)	NA	250-1000
NNH (to cause 1 GS 8-10 CaP)	100	200-333

NNT = number needed to treat; NNH = number needed to harm; NA = not applicable (because incidence of GS ≥7 CaP in PCPT is higher and in REDUCE is lower in the treatment group vs the placebo group).
* Using both the classic (mentioned first) and the modified GS systems.

TREATMENT OF CaP

Neoadjuvant use before radical prostatectomy

Several groups tested the effects of pre-radical prostatectomy (RP) 5α-RI use on CaP tissue. Civantos et al compared the histologic effects of pre-RP finasteride use for 6-24 months with that of 3-month neoadjuvant leuprolide and flutamide.[38] Finasteride caused similar but less pronounced epithelial atrophy and apoptosis, pyknosis, cell vacuolization, and inflammatory cell infiltration, which were evident mainly in Gleason patterns 2 and 3 CaP specimens. Different results were reported by other groups. Yang et al studied CaP needle-biopsied specimens from 53 men who took finasteride 5 mg/d (n = 35) or placebo (n = 18).[39] No significant differences were noted in GS, cancer volume, and percentage of cancer cell atrophy. Bass et al reported that pre-RP finasteride administration for ≥30 days decreased significantly caspase-7 and insulin growth factor binding protein-3 (proapoptotic factors) expression in prostatic tissue compared with placebo.[40]

Studies of neoadjuvant dutasteride reported more consistent findings than for finasteride. Andriole et al randomized 46 men awaiting RP to daily dutasteride 5 mg or placebo for 6-10 weeks.[41] Dutasteride increased apoptosis assessed using terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) and tissue transglutaminase (tTG), reduced microvessel density (MVD), and increased epithelial atrophy. Differences were not statistically significant, except for tTG staining (in dutasteride users ≥45 days) and epithelial atrophy (in the whole treatment group). Cancer volume was 31% lower in the dutasteride group, after normalization for prostate volume. No differences were noted in margin status and rates of capsular penetration.

Iczkowski et al analyzed RP slides in a blinded manner from 35 patients with clinically localized CaP who were treated with dutasteride 5 mg/d (n = 17) and placebo (n = 18) for 5-11 weeks.[42] In CaP tissue, dutasteride caused more reduction in cancer volume ($P = .025$), more epithelial atrophy ($P = .041$), and doubled the

stromal/gland ratio ($P = .046$). No changes were noted in GS between the 2 groups. Margin status and capsular penetration were not reported. Gleave et al randomized 81 men with clinically localized CaP into 3 treatment groups: dutasteride 0.5 mg/d (group 1), dutasteride 3.5 mg (group 2), or no therapy (group 3) for 4 months before RP.[43] In CaP tissue, epithelial atrophy was lower and MVD was higher in the dutasteride groups, but the differences were not statistically significant. The proportions of CaP cells labeled apoptotic, and the differences between the treatment groups, were not consistent between the 2 methods of assessment (tTG and TUNEL). tTG staining was similar between the groups, whereas TUNEL staining demonstrated a significant decrease in apoptosis in dutasteride-treated subjects. Proliferation was increased in dutasteride-treated subjects, although this was only statistically significant in group 1. These results can be explained by the time-dependent effect of dutasteride on apoptosis and proliferation and the difference in staining duration between tTG and TUNEL.[44,45] Increased apoptosis and decreased proliferation occur early after starting antiandrogenic treatment, lasting for a few days to several weeks, after which they return to baseline. tTG staining lasts longer than TUNEL staining. It can be hypothesized that androgen-sensitive cells undergo apoptosis early during treatment, and that subsequent decline in apoptosis and increase in proliferation are caused by the survival of castration-resistant CaP.

Biochemical Failure After Local Therapy With Curative Intent

Finasteride and dutasteride have been tried, singly and in combination with other drugs, in patients with biochemical failure after RP or radiotherapy. The most common combination was 5α-RI and nonsteroidal antiandrogen. Finasteride and dutasteride monotherapy decreased PSA variably. PSA decrease was more frequent and of greater magnitude in patients treated with an antiandrogen and 5α-RI vs 5α-RI alone. However, none of these trials studied the impact on disease-specific or overall survival and none compared 5α-RI mono- or combination therapy with ADT in a randomized fashion.

Barqawi et al administered low-dose flutamide 250 mg/d and finasteride 10 mg/d to 71 men with biochemical failure after local therapy for CaP.[46] Forty-two patients had undergone RP and 29 patients had undergone external beam radiotherapy and none had radiographic evidence of metastasis. At median follow-up of 44 months, 58% achieved PSA $\leq$0.1, 38% had stable PSA $<$0.4, and 8% had stable reduction in PSA $>$50% from baseline. Twenty-one patients (29%) had PSA progression, defined as 3 consecutive PSA rises measured $>$4 weeks apart. Most patients had AEs, which included breast tenderness (90%), gynecomastia (72%), and gastrointestinal disturbances (22%). However, these AEs were mild and well-tolerated by most patients. Another trial compared flutamide 250 mg/d and finasteride 10 mg/d (group A) with low-dose flutamide (250 mg/d, group B) in a prospective nonrandomized fashion in 56 patients with biochemical failure after local therapy for cT1-T3 CaP.[47] PSA suppression was more frequent and of greater magnitude in group A. Mean PSA nadir was 0.6 ng/mL in group A vs 0.99 ng/mL in group B. Complete PSA response, defined as PSA $\leq$0.1 on 2 consecutive assessments after starting protocol treatment, was seen in 36% in group A vs 15% in group B. PSA progression was seen in 36% of group A patients and 60% of group B patients. AEs were similar in the 2 groups.

Oh et al evaluated the combination of flutamide 750 mg/d and finasteride 5 mg/d given sequentially to 20 men either with biochemical failure after radiotherapy or newly diagnosed cN+ or M+ CaP.[48] Flutamide 750 mg/d was administered first until PSA nadired, followed by finasteride 5 mg/d until the second PSA nadir. Patients were continued on the combination until radiologic or PSA progression, when medical or surgical castration was administered. At median follow-up of 88 months, 2 patients were progression-free and 12 patients had undergone castration. Upon castration, all 12 patients exhibited PSA response ($>$50% decline in baseline PSA). However, 11 patients had failed castration at last follow-up. Median protocol treatment progression-free survival was 30 months, median castration-free survival was 37 months, and median CR–CaP-free survival was 49 months. Median duration of response to salvage castration was 12 months, less than primary castration; however, duration of hormonal control with protocol treatment was similar to primary castration. Five-year overall survival was 65%, and 25% of patients were alive without castration 7 years after treatment initiation. Gynecomastia and abnormal liver function tests were the most common AEs; however, they were mild. Sexual function continued to decline with time.

Andriole et al randomized 120 men with biochemical failure after RP performed in the preceding 10 years to either finasteride 10 mg/d or placebo for 12 months.[49] All patients had pT2N+ CaP, PSA 0.6-10 ng/mL, and negative bone scans before treatment initiation. At 12 months, patients on placebo were offered finasteride in an unblinded fashion. PSA decreased in the finasteride group and remained less than or equal to baseline for the first 6 months but then increased. Patients on placebo had a steady but slow PSA increase. When men were switched to finasteride at 12 months, PSA declined for 4 months but then increased. Finasteride treatment delayed PSA progression by 9 and 14 months after 12 and 24 months of treatment, respectively. PSA decline was only seen in stage pT2 and pT3 patients, and was more robust in those with baseline PSA 0.6-1. AEs were few and well-tolerated.

Dutasteride 0.5 mg/d was administered to 35 patients with biochemical failure after RP or radiotherapy for cT1c-T3 CaP.[50] Baseline PSA was 0.4-10 ng/mL (median 4.2). At median follow-up of 27 months, 46% of

patients had PSA response (PSA decline >10% of baseline) and 25% had >50% decline in baseline PSA. PSA progression criteria were met in 25% of patients. At median 24 months, 19 patients (54%) maintained PSA less than baseline. PSA doubling time increased from 8.7 months (before dutasteride) to 15.7 months during treatment.

In combination with intermittent androgen deprivation therapy

Continuous ADT (CADT) was the mainstay of managing advanced CaP. However, ADT is associated with high costs, significant AEs, and inevitable progression to CR–CaP. Intermittent ADT (IADT) has been proposed as an alternative to CADT in an attempt to decrease AEs, improve quality of life (QoL), decrease costs, and prolong time to CR–CaP, without negatively affecting overall survival. Patients are cycled between ADT (on-cycle) and ADT-free periods (off-cycle), according to biochemical (mainly PSA) and clinical criteria that vary across protocols. Preclinical studies suggest that IADT can promote the expansion of androgen-sensitive CaP cells during the off-cycle and may sustain androgen dependence for longer periods.[51] The expected improvement in QoL is caused by T recovery during the off-cycle, which alleviates many of the AEs, and the reduced costs are caused by decreased usage of LHRH analogues and antiandrogens during the off-cycle. Available clinical literature suggests that IADT (compared with CADT) is safe, has fewer AEs, and provides equivalent survival (up to 7 years of follow-up).[52,53] However, long-term efficacy remains unproven.

5α-RI were tested during the off-cycle period of IADT in an attempt to lengthen off-cycle duration and prolong benefits of IADT, without adversely affecting oncological outcomes. Preclinical studies using a LNCaP xenograft tumor model found that finasteride administration during the off-cycle resulted in reduced tumor growth and a 3- to 5-fold increased likelihood of survival at 70 days when compared with results obtained with CADT, CADT + finasteride, and IADT alone, provided that the length of the off-cycle period is fixed.[54] Using the same tumor model, another study found that finasteride administration during the off-cycle doubled the first off-cycle duration.[55] However, there was no significant survival difference between the IADT + finasteride, IADT alone, CADT + finasteride, and CADT groups. Similar results were reported in a clinical study by Scholtz et al, who found that finasteride administration during the off-cycle doubled the duration of the off-cycle from a median of 15 months to a median of 31 months.[56] No difference in time to progression to CR–CaP was found. In a group of 6 patients on IADT followed for 7-10 years, finasteride administration during the off-cycle decreased PSA velocity and increased PSA doubling time from 8 to 45 weeks, regardless of the cycle evaluated.[57] Thus far, data are preliminary and use of 5α-RI in the setting of IADT is investigational.

CR–CaP

CR–CaP was thought for many years to be androgen-independent or hormone-refractory; however, CR–CaP remains AR-dependent and probably AR ligand–dependent in almost all cases.[58] Despite castrate serum levels of T (<50 ng/dL), CR–CaP tissue levels of T and DHT were similar and 80-90% lower compared with their levels in benign prostatic tissue, respectively.[59] CR–CaP synthesizes testicular androgens (T and DHT) in an intracrine fashion from several substrates, such as cholesterol, progesterone, and adrenal androgens.

5α-R isozymes are important in the growth of CR–CaP tissue because they are upregulated in CR–CaP and may contribute to intracrine synthesis of testicular androgens.[60] These enzymes convert progesterone, androstendione, and T into pregnandione, androstenedione, and DHT, respectively. Androstenedione and pregnandione are further converted to DHT via the backdoor pathway.[61]

Clinical trials of 5α-RI monotherapy in patients with advanced CaP showed no improvement in clinical endpoints.[62,63] Combination therapy of 5α-RI with an antiandrogen or ketoconazole and hydrocortisone was tried in CR–CaP as second- or third-line hormonal therapy.[64,65] PSA decreases of variable magnitudes and durations were achieved in >50% of patients. However, none of the combination trials were designed to test the effect on disease-specific or overall survival.

LY320236, a dual 5α-RI, demonstrated activity in CR–CaP.[62] In a phase II study of 51 men with advanced CaP, 4 of 15 men with CR–CaP had >50% decrease in PSA that persisted 56 to >1000 weeks. Most men did not have biochemical or radiographic response. LY320236 was well tolerated with only 3 of 51 patients experiencing reversible NCI grade 3-4 toxicity (ie, diarrhea, elevated liver enzymes); however, drug development was later discontinued because of its teratogenicity. Using the same PSA and radiologic response criteria, a phase II study of dutasteride in 25 men with CR–CaP showed clinically and statistically insignificant outcomes.[63] No patient responded completely. Only 2 of 25 men had a partial response (>50% reduction in PSA compared with baseline) for a mean of 8 months. Stable disease was seen in 9 patients for a mean of 5 months. Disease progressed within 2 months in 14 patients (76%).

In a phase II, single-arm study of 57 patients with CR–CaP, dutasteride added to ketoconazole and hydrocortisone reduced PSA ≥50% from baseline in 56% of patients, responses that lasted for a median of 20 months.[64] Median time to disease progression was 14.5 months, which was better than all prior studies of ketoconazole and hydrocortisone in CR–CaP. All patients experienced AEs with grade 3 toxicity observed in 32% of patients. One patient experienced grade 4 toxicity. Serum dutasteride level was increased by 2- to 3-fold compared with dutasteride monotherapy users, which is consistent with ketoconazole inhibition of CYP 3A4.

Dutasteride was tested as a third-line hormonal therapy in 10 patients with CR–CaP who had failed ketoconazole and hydrocortisone.[65] Dutasteride addition decreased PSA by a median of 16.5% in 80% of patients. Median PSA progression-free survival was 4.9 months. However, no patient achieved >50% reduction in baseline PSA, and no radiographic responses were seen in patients with metastatic disease.

CONCLUSION

CaP Prevention

5α-RI use for 4-7 years can reduce the overall risk of biopsy-detectable CaP by 23-25%. All of the prevented cases are either low-grade (PCPT) or GS ≤3 + 4 = 7 CaP (REDUCE). It is unclear whether the increased risk of high-grade CaP in both trials is real or artifact. Nevertheless, this risk is low.

CaP Treatment

Treatment of CaP with 5α-RI yielded variable biochemical responses, without meaningful clinical benefits. Therefore, 5α-RI appears to have no role in treatment of any stage of CaP.

Future Trials

Trials are underway to better define the role of 5α-RI in CaP prevention and treatment (http://www.clinicaltrials.gov). Results from ARI40006 (2-year follow-up study of REDUCE participants who received dutasteride or placebo), ARTS (biochemical failure after local treatment with curative intent), and AVO 108943 (bicalutamide and dutasteride vs bicalutamide and placebo in CR–CaP) are awaited.

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