Dutasteride and Enzalutamide Synergistically Suppress Prostate Tumor Cell Proliferation

Agus Rizal A. H. Hamid, Gerald W. Verhaegh, Frank P. Smit,*
Cindy van Rijt-van de Westerlo, Inna Armandari, Andre Brandt,
Fred C. G. J. Sweep, John P. M. Sedelaar and Jack A. Schalken†

From the Departments of Urology (ARAHH, GWV, CvR-vdW, IA, JPMS, JAS) and Laboratory Medicine (AB, FCGJS), Radboud University Medical Center, Radboud Institute for Molecular Life Sciences (ARAHH, GWV, CvR-vdW, IA, JAS) and NovioGendix (FPS), Nijmegen, The Netherlands, and Department of Urology, Ciptomangunkusumo Hospital, Faculty of Medicine, University of Indonesia (ARAHH), Indonesia

Purpose: Dihydrotestosterone is the main active androgen in the prostate and it has a role in prostate cancer progression. After androgen deprivation therapy androgen receptor signaling is still active in tumor cells. Persistent intratumor steroidogenesis and androgen receptor changes are responsible for this continued activity, which influences the efficacy of prostate cancer treatment. We hypothesized that combining a 5α-reductase inhibitor and an antiandrogen would block intratumor androgen synthesis and androgen receptor protein activity. Thus, it would act synergistically to reduce tumor cell proliferation.

Materials and Methods: The expression level of 5α-reductase and androgen receptor in endocrine therapy naïve prostate cancer and castration resistant prostate cancer tissues, and cell line models was determined by microarray and quantitative polymerase chain reaction analysis. Intracellular androgen was measured with radioimmunoassay. Tumor cell proliferation was determined using coloric MTT assay. The synergistic effects of combination treatments on tumor cell proliferation were calculated using the Chou-Talalay equation.

Results: In all prostate cancer cases 5α-reductase-1 and 3 were up-regulated. Androgen receptor was up-regulated in metastatic prostate cancer and castration resistant prostate cancer cases. The 5α-reductase inhibitor dutasteride effectively decreased dihydrotestosterone production in prostate cancer and castration resistant prostate cancer cell lines. Furthermore, dutasteride combined with the novel antiandrogen enzalutamide synergistically suppressed endocrine therapy naïve prostate cancer and castration resistant prostate cancer cell proliferation.

Conclusions: In this study the combination of a 5α-reductase inhibitor and (novel) antiandrogens synergistically inhibited tumor cell proliferation. These findings support clinical studies of combinations of a 5α-reductase inhibitor and (novel) antiandrogens as first line treatment of prostate cancer and castration resistant prostate cancer.

Key Words: prostatic neoplasms; prostatic neoplasms, castration-resistant; dutasteride; MDV 3100; antineoplastic combined chemotherapy protocols

Abbreviations and Acronyms

ADT = androgen deprivation therapy
AR = androgen receptor
BPH = benign prostatic hyperplasia
CI = combination index
CRPC = castration resistant PCa
CSS = charcoal stripped serum
DHEA = dehydroepiandrosterone
DHT = dihydrotestosterone
PCa = prostate cancer
PCR = polymerase chain reaction
SRD5A = 5α-reductase
T = testosterone

Accepted for publication September 8, 2014.
Study received Radboud University Medical Center local ethical committee approval.
Supported by European Commission FP7 Marie Curie ITN Contract 238278 and GlaxoSmithKline (ARI114532) as part of PRO-NEST (Prostate Research Organizations-Network of Early Stage Training).
* Financial interest and/or other relationship with Novogendix.
† Correspondence: 267 Experimental Urology, Radboud University Medical Center, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands (e-mail: Jack.Schalken@radboudumc.nl).

DIHYDROTESTOSTERONE, the main active androgen in the prostate, is essential for proper prostate development. PCa initiation and progression also depend on DHT activity.[1] ADT, which has been used since the 1990s,

0022-5347/15/1933-1023/0
THE JOURNAL OF UROLOGY®
© 2015 by AMERICAN UROLOGICAL ASSOCIATION EDUCATION AND RESEARCH, INC.
http://dx.doi.org/10.1016/j.juro.2014.09.021
Vol. 193, 1023-1029, March 2015
Printed in U.S.A.

became standard treatment for advanced PCa. However, lower DHT (about 15% of baseline) in prostate tissue after ADT is still sufficient to activate AR and persistent AR signaling underlies the emergence of CRPC within 2 to 3 years after starting ADT.[1,2]

It was recently found that low DHT levels in the prostate after ADT are a result of intratumor androgen synthesis (steroidogenesis). Prostate tumor cells acquire the ability to convert androgen precursors such as adrenal DHEA into T and DHT.[3] Many studies show that SRD5A activity is crucial for these conversions (fig. 1, *A*). Three isoforms of SRD5A enzyme were reported, of which SRD5A1 and SRD5A3 are up-regulated in PCa compared to benign prostate tissue.[4–7] The dual (type 1 and 2) SRD5A inhibitor dutasteride is FDA (Food and Drug Administration) approved for BPH and this drug may also be effective for advanced PCa.[8]

Several studies showed that combining castration with antiandrogens resulted in only limited improvement in the therapeutic efficacy of advanced PCa compared to castration alone. This may be explained by the low affinity of classic antiandrogens such as flutamide and bicalutamide for the mutated AR. A recent improvement was the development of the more potent, effective AR antagonist enzalutamide. Enzalutamide binds with up to 8 times greater affinity to AR than classic antiandrogens.[2]

Due to the failure of current first line treatments to effectively target AR signaling new drugs or protocols are urgently needed to treat advanced

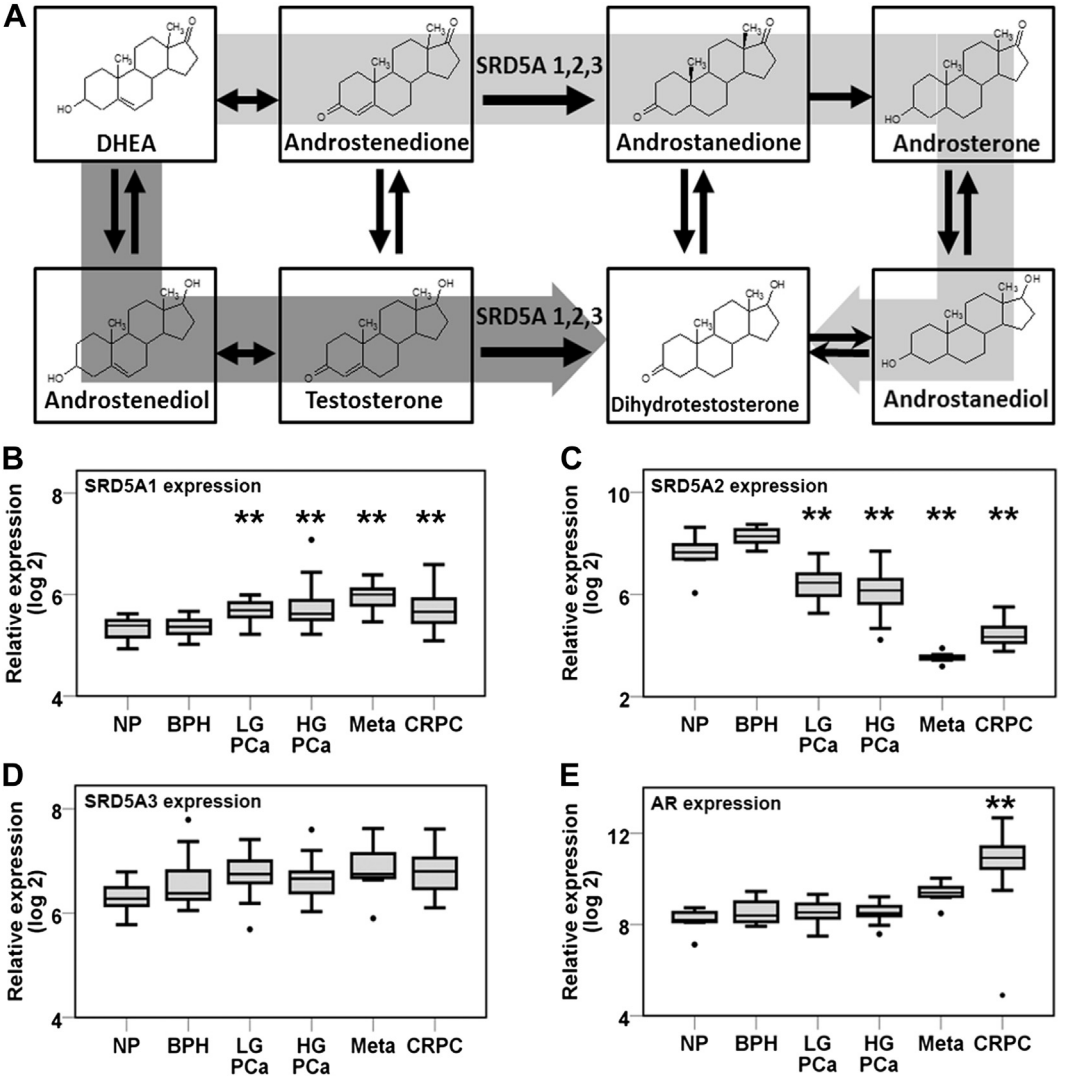

Figure 1. SRD5A function in DHT production and expression in clinical samples. Metabolic conversion of DHEA into DHT (*A*). In classic (dark gray arrow) and back door or alternative (light gray arrow) pathways SRD5A enzyme has central role in DHT production. Relative mRNA expression in prostate tissue samples (*B* to *E*). *NP*, normal prostate. *LG*, low grade. *HG*, high grade. *Meta*, PCa metastasis. One-way ANOVA and Dunnett correction test with normal prostate as control. Asterisks indicate $p<0.05$.

Download English Version:

https://daneshyari.com/en/article/3859502

Download Persian Version:

https://daneshyari.com/article/3859502

Daneshyari.com