Hormonal therapy for prostate cancer: Current topics and future perspectives: Editorial

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Hormonal therapy for prostate cancer: Current topics and future perspectives: Editorial

Atsushi Mizokami, MD, PhD

Department of Integrative Cancer Therapy and Urology,
Kanazawa University Graduate School of Medical Sciences

13-1 Takaramachi, Kanazawa, 920-8640 Japan

Tel: +81-76-265-2393 FAX: +81-76-222-6726

mizokami@med.kanazawa-u.ac.jp

Running title: Hormonal therapy for prostate cancer: Current topics and future perspectives: Editorial

Prostate cancer (PCa) is the most common malignancy and the second leading cause of cancer-related death of men in the United States. Since advanced PCa is initially dependent upon androgens, androgen-deprivation therapy (ADT) with LH-RH agonist and antiandrogen (bicalutamide or flutamide) is the first choice for advanced PCa. Unfortunately, after an initial response to ADT, PCa eventually does not respond to ADT and progresses into what is termed an androgen insensitive state against LH-RH agonist and antiandrogen.

Multiple molecular mechanisms that could account for the development of resistance to ADT have been proposed that typically invoke the androgen receptor (AR) as a key mediator in the progression of PCa.[1] Moreover, alterations of AR itself, which are either absent or at low frequency in the original androgen-dependent state, result in an androgen-hypersensitive situation where stimulation of PCa growth occurs at castrate levels of androgens. Therefore, in addition to its normal ligands, testosterone (T) and dihydrotestosterone (DHT), both androstenediol, a precursor of T, can activate the AR and stimulate the proliferation of LNCaP cells which have a mutated AR.[2] T and the more active androgen DHT are important factors in PCa progression. These hormones are still present in PCa tissue after ADT. Specifically, when

PCa patients are treated with ADT, serum T and DHT decreases to less than one-tenth of pretreatment levels. However, T and DHT in PCa tissue are still present at 20 to 40% of pretreatment values.[2]

T and DHT in PCa tissue after medical or surgical castration are synthesized locally in the prostate from dehydroepiandrosterone (DHEA) of adrenal origin.[3] The metabolism from DHEA to DHT in peripheral target tissues depends upon the level of expression of various steroidogenic enzymes in the specific cell types of these tissues. Adrenal DHEA is converted to T by 17 β -hydroxysteroid dehydrogenase (17 β -HSD) and 3 β -HSD. And T is then converted to DHT by 5 α -steroid reductase (SRD5A) in the prostate. Currently, two types of 3 β -HSD, fifteen types of 17 β -HSDs and 3 types of SRD5A have been identified and localized in various peripheral tissues, including the prostate, with specific expression patterns in each tissue.[4 5] Fung et al. have observed increased expression of AKR1C3 (type 5 17 β -HSD) in PCa tissue while Stanbrough et al. confirmed that ADT-resistant PCa and bone marrow metastases expressed increased levels of multiple genes responsible for androgen metabolism (HSD3B2, AKR1C3, SRD5A1, AKR1C2, AKR1C1 and UGT2B15).[6 7] These studies provide support for the concept that PCa tissues can perform local biosynthesis of T and DHT resulting in activation of the AR.

Recently, we demonstrated that T and DHT synthesized from DHEA in stromal cells activated AR in PCa epithelial cells in a paracrine fashion and stimulate PCa proliferation. Thus adrenal androgen DHEA contribute to the development of ADT resistance in PCa.[8]

Therefore, alternative antiandrogen therapy (this is described in other section) is one of alternative strategies to extend the period when normal ADT (first-line hormonal therapy) is effective. Recently, second generation of antiandrogens, MDV3100 and RD162, of affinity to AR is 10 times more than bicalutamide were developed. These drugs not only block DHT binding to AR but also reduce the efficiency of its nuclear translocation. In phase I/II trial using MDV3100, 22 out of 30 castration resistant PCa (CRPC) had a sustained decline in PSA for at least 12 weeks.[9] If these second generation antiandrogen are clinically available without severe adverse effect, these will be useful as another alternative antiandrogen therapy.

Since DHT is synthesized in prostate cancer tissue as described above, SRD5A inhibitor is also a candidate to inhibit progression after alternative antiandrogen therapy. SRD5A inhibitor, dutasteride repressed DHT synthesis and inhibit AR activity in LNCaP cells cocultured with stromal cells in vitro. Indeed, Shah reported phase II study using 3.5 mg dutasteride for CRPC. Of the 25 men 14 had disease progression by 2 months, 9 had stable disease, 2 had a partial

response and none had a complete response. Now, The Therapy Assessed by Rising PSA (TARP) study is ongoing to investigates dutasteride in combination with bicalutamide to prevent or delay disease progression in patients with castrate-refractory prostate cancer (CRPC) after initial androgen deprivation therapy.

Since the source of DHEA is derived from adrenal gland, new DHEA synthesis inhibitor abiraterone in place of ketokonazole may be effective for CRPC. Abiraterone inhibit CYP17 that is associated with DHEA synthesis from cholesterol in adrenal gland. A decline in PSA of 50% was observed in 28 (67%) of 42 phase II patients, and declines of 90% were observed in eight (19%) of 42 patients in CRPC. Now randomized phase III study comparing abiraterone plus prednisone versus prednisone plus placebo in CRPC patients who have previously received docetaxel is progressing.[10]

In conclusion, we may obtain new hormone therapeutic drugs for the recurrence prostate cancer several years later. It is necessary to evaluate it whether we should use them in a timing that is a combination to use those medicine for, or we should use them sequentially.

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Figure legend

New hormonal therapies for recurrence of prostate cancer

Figure Mizokami