INTRODUCTION

Prostate specific antigen (PSA) is a useful biomarker for prostate cancer (PCa). It has been shown that serum PSA level is proportional to tumor volume and correlates positively with the clinical stage of the disease. Furthermore it is used for monitoring treatment response, prognosis, and progression in PCa patients [1,2]. The PSA transcriptional control is initially androgen-regulated and decreased after androgen deprivation therapy (ADT) [3]. Patients with advanced stage prostate cancer initially respond well to ADT, but then progress to castration-resistant prostate cancer (CRPC), which is accompanied with high mortality rate [4].

The J-CAPRA score is a novel, validated score for predicting outcomes among patients undergoing primary ADT across the full spectrum of risk and stage, including advanced disease [5]. Nadir PSA level after ADT has been reported as an important tool to predict progression in patients with metastatic PCa [6-8]. Recently, combination of lower PSA nadir level and longer time to PSA nadir (TTN) after ADT is shown to be associated with longer progression-free and overall survival in metastatic PCa patients [9-18].

The objectives of this article is to review the influence of PSA kinetics on disease progression, especially focusing on the combination of PSA nadir level and TTN, to discuss the mechanisms, and to propose appropriate management for patients with advanced PCa.
BIOLOGY OF PSA

PSA is an androgen-regulated serine protease and member of the tissue kallikrein family of protease [19]. Prostate glands in human consist of a single layer of secretory epithelial cells, which are surrounded by a continuous layer of basal cells and a basement membrane. PSA is produced by secretory epithelial cells in prostate gland and is secreted directly into the lumen. A characteristic of prostate cancer is disruption of the basal cell layer and basement membrane, and this loss of normal glandular architecture results in the increase in serum PSA [20-22].

Transcription of PSA gene is regulated by androgens through the androgen receptor (AR) [23]. The AR is a steroid hormone receptor that binds as a homodimer to the specific DNA sequence, termed androgen-responsive elements (AREs). A consensus ARE is located at -156 to -170 from the transcriptional start site of the PSA gene [24]. The PSA distal enhancer is located approximately 4.2 kb upstream of the transcription start site which is a region containing single strong consensus ARE (ARE III). Furthermore, the presence of multiple additional weak non consensus AREs have demonstrated by binding studies. The cooperative binding of multiple ARs to this region likely accounts for its strong androgen-dependent activity [22,25-28].

The decrease in PSA levels after ADT is certainly resulted from tumor cell death and/or decreased expression of AR-stimulated PSA in surviving tumor cells. As a result, ADT may in some cases have greater effects on PSA production than on tumor survival. Combined castration and AR antagonist treatment results in more rapid decrease of PSA and lower PSA nadir than castration alone; however, this does not translate into a significant improvement in survival [22,29].

AR is activated by protein kinase A and/or protein kinase C pathway in the absence of androgen and the androgen-independent induction of PSA gene expression in LNCaP cells is regulated by AR-dependent pathway [30-32]. Mitogen-activated protein kinase signaling may also regulate PSA transcription in androgen-independent manner [33].

MECHANISMS OF PROGRESSION TO CRPC AFTER ANDROGEN-DEPRIVATION THERAPY

Free Testosterone enters prostate cells and gets converted to dihydrotestosterone (DHT) by 5α-reductase, which in turn binds to the AR. The AR is a nuclear transcription factor that can activate and regulate the expression of several genes involved in growth and proliferation [34-36]. ADT is the standard therapy for advanced PCa patients. However patients invariably relapse with progression to become CRPC. Studies show that most of the CRPC still express AR, and AR gene amplification occurs in about one third of CRPC patients [37,38]. Thus, AR transcriptional activity and signaling may increase under an androgen-depleted condition in CRPC. Several molecular mechanisms can lead to the AR reactivation after ADT.

AR overexpression

Increased AR expression may enhance any weak residual AR activity that remains after castration, and can increase the growth of PCa cell line in castrated mice [39]. AR amplification was found in approximately 25%-30% of androgen-independent tumors but not found in any untreated PCa samples, suggesting that AR amplification is resulted from ADT [40]. Increased AR expression sensitizes PCa cells to low levels of androgen, and help PCa cells survive and proliferate in environments with lower androgen concentrations [41].

AR mutation

The frequency of AR mutations in patients treated initially with ADT is quite low, whereas increased AR mutation has been found in the patients with metastatic disease who were treated with ADT and in CRPC patients [42-43]. The AR mutations in CRPC can enhance AR activation by weak adrenal androgens and other steroid hormones such as progesterone, estradiol, and cortisol. These mutations may also alter AR responses to flutamide and bicalutamide, which are the AR antagonists and used in combination with castration as initial hormone therapy for PCa. Thus, these drugs act as potent agonists and clinically related to antiandrogen withdrawal syndrome [44-47].

AR splice variants

AR splice variants have been recently identified, and are found to be overexpressed in CRPC, although they have not been detected in normal tissues. A common characteristic of these variants is the elimination of a ligand-binding domain. PCa cells with AR splicing variants can bypass the need for androgens, because the AR can become constitutively active [48-50].

In addition to alterations in AR expression or structure described above, there are several factors that contribute to activation of AR despite castration levels of serum androgens.

Changes in steroid metabolism

De novo synthesis of androgens within the PCa cells may play an important role in activating AR. Overexpression of enzymes involved in steroid biosynthesis pathway have been observed in CRPC samples [51]. Montgomery revealed that CRPC tumors have increased expression of multiple enzymes responsible for the synthesis of adrenal androgens. They also reported high concentrations of intratumoral androgens in castrate-resistant xenografts lacking the adrenal cytochrome p450, family 17, subfamily A, polypeptide 1 (CYP17A) gene, which is essential for the androgen synthesis pathway in adrenal gland [52]. More recently, Hofland concluded that intratumoral steroid biosynthesis may be less important than the production of intraprostatic testosterone and DHT from circulating adrenal androgens in PCa cells for CRPC progression, suggesting the blockade of CYP17 as a therapeutic target for CRPC [53]. Increased AR expression and equivalent levels of PSA expression in CRPC were observed compared with primary PCa and benign prostate, and these findings may attribute to elevated levels of intratumoral testosterone levels [53].

Thus, CRPC cells may perform intracellular synthesis of testosterone and DHT from weak adrenal androgens and may be able to synthesize androgens from cholesterol.
REGULATION OF COACTIVATOR AND COREPRESSOR

AR regulates gene expression through recruitment of a series of coregulator complexes. These coregulators can function either as coactivators enhancing transcription or as corepressors suppressing transcription [54]. Among these coactivators, p160 coactivators, SRC-1 and SRC2 (TIF2), can increase AR transcriptional response to low levels of androgen. The SRC2 levels are repressed by androgens, hence ADT can induce SRC2 levels [55,56].

Nuclear receptor corepressor (NCoR) and its homolog silencing mediator for retinoid and thyroid hormone receptor (SMRT) are well characterized AR co repressors, and both of them can recruit histone deacetylases, which promote chromatin packing, resulting in reduced transcriptional activity [57]. Thus, increases in expression of coactivators, or decreases in expressions of corepressors during ADT play, in part, a role in increased AR activity and progression to CRPC.

Alter cell signaling pathway

Activation of the PI3 kinase/AKT and Ras-Raf-MAP kinase pathway, and increased expression of receptor tyrosine kinases such as HER2/Neu/Erb2 are observed in more aggressive PCa and in CRPC [58-61]. Many in vitro and in vivo studies have shown that activation of these kinase pathways can enhance response to low levels of androgen [58,60,62-64]. However, the effects of AR activation by these kinase pathways appear to be mediated through phosphorylation of coactivators, rather than through AR phosphorylation itself [65]. Akt1 and Src, which are tyrosine kinases, can phosphorylate AR directly, and enhance AR responses to low levels of androgen [66-68].

Many of the changes described above can contribute to AR activation and AR hypersensitivity to adapt to the low levels of androgens, and could be the mechanisms of inducing CRPC and rising PSA levels in castrated environment.

PSANADIRAND TTN IN ANDROGEN-DEPRIVATION THERAPY

Nadir PSA level after hormone therapy has been reported as an important tool to predict progression in patients with metastatic PCa [7,8]. The nadir PSA levels of 0.2 ng/ml was suggested to be the optimal threshold for predicting to CRPC [9,13] and survival [11,14,15,17,18]. It is generally expected that a more rapid reduction of PSA in response to ADT would correlate with more prostate cancer cell death followed by higher survival, and shorter TTN correlated with longer remission periods [69]. A few studies with ADT for postoperative and postradiation PSA failure have also reported that longer TTN was predictive of high risk of cancer specific survival [70,71]. In contrast, several recent studies have demonstrated that a longer TTN is correlated with longer progression free survival [9-13]. These finding seems counter-intuitive.

More recently, combination of lower PSA nadir level and longer time to PSA nadir (TTN) after hormone therapy is associated with longer progression-free and overall survival in metastatic PC patients (Table 1) [9-18]. As for progression, Morote reported that a PSA nadir ≤ 0.2ng/ml and TTN ≥ 12 months was associated with a low risk of PSA progression with metastatic PC patients [9]. Hori have reported that PSA nadir < 1ng/ml and TTN > 12 months associated with low risk of biochemical relapse in patients with bone metastasis, and PSA nadir < 0.1ng/ml and TTN >24 months associated with low risk of biochemical relapse in patients without bone metastasis [11]. However, these studies included various clinical stages and patients with different types of pre-treatment such as radical prostatectomy or radiotherapy. The limitation of their studies could be the patient’s classification. Their patients were stratified in two groups by PSA nadir level or TTN. Inadequate PSA responders with shorter TTN due to a little PSA decline from high level of PSA, which is obviously associated with poor progression, might possibly be included in shorter TTN group.

Interestingly, Huang et al. stratified in four groups by combination PSA nadir level and TTN. They demonstrated PSA nadir ≥ 0.2ng/ml and TTN < 10 months had significant shorter time to disease progression for advanced or metastatic patients. However, their study did not demonstrate that prolonged TTN was correlated with longer progression free survival in adequate PSA responders (PSA nadir ≤ 0.2) because they included patients with different types of pre-treatment such as radical prostatectomy or radiotherapy [12]. We also stratified in four groups by combination PSA nadir level and TTN, and demonstrated that longer TTN identified patients with prolonged progression in both groups with PSA nadir ≤ 0.2 and > 0.2. The combination of lower PSA nadir (lower than 0.2 ng/ml) and longer TTN (more than 9 months) during initial hormone therapy is the most important early predictors for overall survival for advanced PCa patients with bone metastasis at diagnosis [15]. Similar results in patients with metastatic PCa have been reported [17,18]. We have also found that cut-off value of TTN in patients without bone metastasis is significantly longer than those with bone metastasis, that is, the cut-off value of TTN could be inversely correlated with disease progression (optimal cut-off value of TTN is > 11 months in advanced PCa patients without bone metastasis and > 8 months in those with bone metastasis) [16].

Taken together, a rapid decrease of PSA expression during ADT strongly indicates more aggressive disease, and by contrast, prolonged TTN is associated with low risk of progression. According to the studies that have examined both PSA nadir and TTN as prognostic factors, the optimal threshold of PSA nadir may be 0.2 ng/ml, and that of TTN may be approximately 10 months (Table). Thus the combination of PSA nadir and TTN following ADT is one of the important early predictors for progression and survival in advanced PCa patients, and could be helpful for decision making of treatment strategy.

Possible mechanisms responsible for the association of shorter TTN with poor prognosis

The mechanisms why shorter TTN is correlated with poor prognosis of advanced PCa after ADT remain unknown. We discussed the three possible explanations [16].
First, the androgen-depletion of androgen-dependent PCA cells results in early G1 arrest, characterized by reduced cyclin-dependent kinase activity, and unphosphorylated retinoblastoma tumor suppressor protein [72]. Two types of PCA cells may exist, one with characteristic of differentiating to CRPC during cell cycle arrest with rapid reduction of PSA induced by ablation of androgen receptor, and the other gradually going to apoptosis (cell death) after cell cycle arrest with slow reduction of PSA. The former would be rich in shorter TTN group, and the latter would be originally present in a large number in advanced PCa patients. Androgen-producing, can grow in low androgen environment, and would be inversely correlated with disease progression, and the cutoff PSA value of TTN could be 0.2 ng/ml. (HR0.31, 95%CI 0.16-0.62)

Abbreviations: ADT: Androgen Deprivation Therapy; MAB: Maximal Androgen Blockade; TTN: Time To PSA Nadir; LHRH: Luteinizing Hormone-Releasing Hormone; HR: Hazard Ratio; CI: Confidence Interval; RP: Radical Prostatectomy; RT: Radiation Therapy; AIP: Androgen Independent Progression; PCa: Prostate Cancer; ACM: All-Cause Mortality; PCSM: Prostate Cancer-Specific Mortality

Table 1: Summary of studies examining combination of PSA nadir and TTN after ADT as makers for outcomes.

<table>
<thead>
<tr>
<th>Studies</th>
<th>Patients</th>
<th>Treatment</th>
<th>Cutoff thresholds</th>
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<tr>
<td>Morote [9]</td>
<td>N=283 (98; locally advanced; 185; metastatic)</td>
<td>Orchidectomy or MAB</td>
<td>0.2 12</td>
<td>The ability to achieve an undetectable nadir PSA and the time to reach it are the most significant predictors of the time to AIP in patients with locally advanced and metastatic prostate cancer under androgen suppression as a single therapy. Nadir PSA (OR6.072; 95%CI 2.207-9.432; P=0.001), TTN (OR3.112; 95%CI 2.207-4.390; P=0.001)</td>
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<td>Morote [10]</td>
<td>N=185 metastatic PC</td>
<td>Orchidectomy or LHRH agonist with antiandrogen</td>
<td>2 9</td>
<td>AIP was independently predicted by nadir PSA and TTN. Nadir PSA (OR3.22; 95%CI 1.81-5.71; P=0.001), TTN (OR2.84; 95%CI 1.94-4.17; P=0.001)</td>
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<tr>
<td>Choueiri [11]</td>
<td>N=179 metastatic hormone-sensitive PC; 47.5% had prior RP or RT</td>
<td>LHRH agonist or Orchidectomy with or without antiandrogen</td>
<td>0.2 6</td>
<td>A faster time to reach a PSA nadir post-ADT initiation is associated with shorter survival duration in men with metastatic hormone sensitive PC. The relationship prolonged TTN and an improved survival became apparent in patients with a nadir=0.2 ng/ml. (HR0.31, 95%CI 0.16-0.62)</td>
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<td>Hori [12]</td>
<td>N=155 (46; with bone metastasis, 109 without bone metastasis)</td>
<td>LHRH agonist or Orchidectomy with or without antiandrogen</td>
<td>0.1 (without bone metastasis) 24 (without bone metastasis)</td>
<td>PSA nadir and TTN are key predictors of a good outcome in men with localized or locally advanced PC and without bone metastasis. Nadir PSA (HR1.21; 95%CI 1.09-1.35; P=0.001), TTN (HR0.90; 95%CI 0.88-0.95; P=0.001)</td>
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<td>Huang [13]</td>
<td>N=650 advanced or metastatic PC; 35% had prior RP or RT</td>
<td>LHRH agonist or Orchidectomy with or without antiandrogen</td>
<td>0.2 10</td>
<td>PSA nadir and TTN are significant predictors of disease progression for PC patients receiving ADT. Nadir PSA (HR2.38; 95%CI 1.91-2.97; P=0.001), TTN (HR1.31; 95%CI 1.07-1.61; P=0.009)</td>
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<tr>
<td>Huang [14]</td>
<td>N=650 advanced or metastatic PC; 35% had prior RP or RT</td>
<td>LHRH agonist or Orchidectomy with or without antiandrogen</td>
<td>0.2 10</td>
<td>Higher PSA nadir and shorter TTN had significantly high risk of PCSM and ACM compared to those with lower PSA nadir and longer TTN. PCSM (HR6.30; 95%CI 1.30-13.23; P=0.001), ACM (HR4.79; 95%CI 2.63-8.73; P=0.001)</td>
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<tr>
<td>Sasaki [15]</td>
<td>N=87 PC patients with bone metastasis</td>
<td>LHRH agonist or Orchidectomy with antiandrogen</td>
<td>0.2 9</td>
<td>Lower PSA nadir and prolonged TTN are the most important early predictors for longer survival. Nadir PSA (HR3.73; 95%CI 1.54-9.03; P=0.003)</td>
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<tr>
<td>Sasaki [16]</td>
<td>N=184 advanced PC (101; with bone metastasis, 83; without bone metastasis)</td>
<td>LHRH agonist or Orchidectomy with antiandrogen</td>
<td>0.2 8 (with bone metastasis) 11 (without bone metastasis)</td>
<td>Longer TTN is strongly associated with a low risk of disease progression, and the cutoff PSA value of TTN could be inversely correlated with disease progression. Nadir PSA (HR3.99; 95%CI 2.46-6.46; P&lt;0.001), TTN (HR4.27; 95%CI 2.65-6.88; P&lt;0.001) with bone metastasis; Nadir PSA (HR24.6; 95%CI 19.62-62.8; P&lt;0.001), TTN (HR4.60; 95%CI 1.97-10.7; P&lt;0.001)</td>
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<td>Hong [17]</td>
<td>N=131 metastatic, hormone-sensitive PC</td>
<td>LHRH agonist or Orchidectomy with antiandrogen</td>
<td>0.2 8</td>
<td>Patients with higher PSA nadir and shorter TTN had the worst progression free survival (HR14.098; 95%CI 7.399-26.864; P&lt;0.001) and cancer-specific survival (HR14.050; 95%CI 4.974-39.692; P&lt;0.001) compared with those with lower PSA nadir and longer TTN.</td>
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<td>Zhang [18]</td>
<td>N=332 untreated advanced or metastatic PC</td>
<td>LHRH antagonist or Orchidectomy with flutamide</td>
<td>0.2 10</td>
<td>PSA nadir and TTN were the independent risk factors for predicting biochemical failure, overall survival and cancer-specific survival. The best cutoff of PSA nadir was 0.2 ng/ml (sensitivity 65.7%, specificity 80.6%) and the best cutoff of TTN was 10 months (sensitivity 71.6%, specificity 63.9%).</td>
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and androgen independent) is available for experimental research [73,74]. The rapid reduction of PSA simply may be affected by down-regulation of PSA expression, which is regulated by androgen through AR, rather than PC cell death. Furthermore, PSA reduction by androgen deprivation might be faster in these cells than in androgen-dependent prostate cancer cells.

The proteolytic capacity of PSA in tumor microenvironments has the potential to cleave a number of proteins such as insulin-like growth factor binding protein-3 (IGFBP-3) that may influence PCa development or progression [17]. IGFBP-3 is a growth factor for PCa and an increase of serum IGF-1 have been shown to be a risk for PCa [75,76]. IGFBP-3 is the major serum binding protein for IGF-1 and its cleavage by PSA decreases IGF-1 binding [77,78]. Therefore, the third mechanism might be that PSA and/or unknown factor produced by androgen-dependent PCa cells might play a role of inhibiting the growth of androgen-independent PC cells. Thus, an adequate environment for growing androgen-independent PCa cells might be induced by a rapid removal of androgen-dependent PCa cells.

5α-reductase inhibitor dutasteride reduced the risk of incident prostate cancer; however, detection of Gleason 8-10 prostate cancer was significantly higher in the dutasteride group than in the placebo group [79]. In metastatic CRPC patients treated with docetaxel, shorter TTN is an independent predictor for shorter duration of response and shorter progression free survival in metastatic CRPC patients treated with docetaxel [80]. These findings might support our third hypothesis described above. Further studies will be needed to prove these hypotheses.

Potential ADT strategies for advanced PCa patients

Based on the finding that combination of lower PSA nadir and prolonged TTN is associated with low risk of progression, intermittent ADT might be one of the ideal hormone therapy strategies for preventing the progression to CRPC, since longer TTN could be obtained by intermittent ADT. Randomized studies completed to date indicate that intermittent ADT might be equivalent to continuous ADT [81]. However, randomization criteria for this trial is a PSA decline of 80%, or to < 4ng/ml on initial 3-month continuous ADT. Earlier start of intermittent ADT might prolong TTN followed by good prognosis.

Gonadotropin-releasing hormone (GnRH) antagonist induced testosterone and suppressed PSA significantly faster than GnRH agonist [82]. Therefore, it will be interesting to see if there is the difference in progression between the patients treated either with GnRH antagonist or GnRH agonist [83].

It appears that ADT may play a critical role in developing CRPC by several mechanisms of enhancing AR activities in low androgen condition described earlier. Furthermore, it is considered that CRPC may be easily induced in advanced PCa patients with shorter TTN during ADT. Therefore, ADT (or intermittent ADT) in combination with new agents focusing on novel ways to suppress AR signaling such as abiraterone (CYP17A1 inhibitor) or enzalutamide (a novel AR antagonist) [84], might contribute to good prognosis especially in advanced PCa patients with shorter TTN. Thus, the tailor-made ADT based on the results of combination of nadir PSA level and TTN might be a useful treatment strategy for advanced PCa patients.

REFERENCES

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