



IS TESTOSTERONE PROGNOSTIC IN PROSTATE CANCER TREATMENT? THE UROLOGICAL STANDPOINT.

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SUMMARY – Prostate cancer (PC) is known as an androgen-dependent tumor with testosterone as its natural growth factor, its action is mediated by the androgen receptor (AR) important for the biology and progression of PC. During aging a progressive decline in testosterone levels begins, caused by disability of aged Leydig cells to produce testosterone in response to luteinizing hormone. Surgical treatment of PC can influence the hypothalamic-pituitary-gonadal axis with less impact on it compared to patients treated with radiation. Patients with pre-operative low baseline testosterone level had mean Gleason score higher and AR expression was higher; significantly lower testosterone levels were recorded in patients with lymph node metastases. But some data are conflicting, and some results are opposite to those mentioned before. These data show that there is no significant association between all sex hormone in men and lethal PC or total mortality. In patients with metastatic PC, results showed that elevation of baseline androstenedione levels was predictive of prostate-specific antigen (PSA) response; higher baseline androstenedione levels were associated with an improved overall survival. In these patients, the relationship between serum testosterone and PC prognosis varies in different clinical settings and according to androgen deprivation therapy administration.

Key words: *Prostate Cancer, Androgen Deprivation Therapy, Metastatic Prostate Cancer, Serum Testosterone*

Introduction

Prostate cancer (PC) is one of the most frequent cancers in male population (second place by incidence, behind lung cancer) and also one of the leading causes of cancer-related deaths.¹ During the last few decades, use of prostate specific antigen (PSA) testing has led to an increase in incidence but also significant proportion of patients was diagnosed in a much earlier stage of disease which allows wider treatment options and better prognosis. However, for patients diagnosed with recurrent or disseminated disease, treatment options are more limited, and prognosis is worse.^{2,3}

Prostate cancer is known as an androgen-dependent tumor with testosterone as its natural growth factor. Its

action is mediated by the androgen receptor (AR) which is hormone-activated transcription factor important for the biology and progression of PC.⁴ Testosterone can stimulate PC progression, it has been observed in PC patients with „flare phenomenon“ when luteinizing hormone-releasing hormone (LHRH) analog administration causes transient increase in serum testosterone levels.⁵ Androgen deprivation therapy (ADT) plays the central role in PC treatment and leads to beneficial responses in most patients with advanced disease.⁶ Unfortunately, some patients develop the castration-resistant disease as a result of AR amplification as the most important molecular alteration.⁴

Treatment options for localized PC are surgery (radical prostatectomy) or radiation, with or without ADT, and treatment options for locally advanced and disseminated PC are radiation with ADT, ADT alone or in combination with chemotherapy.⁴

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The aim of this review is to compare prognostic value of testosterone in treatment of localized PC, advanced PC either before or during ADT, and in castration-resistant PC.

Testosterone decline with age

Androgens are essential for male sexual maturity. Testosterone regulates muscle development and gonadotropin secretion; dihydrotestosterone (DHT) regulates spermatogenesis and all other factors of male sexual maturity (hair growth, acne, male pattern baldness, etc.).⁷ Pituitary luteinizing hormone (LH) stimulates Leydig cells in the testicular interstitium to produce testosterone. Progressive decline in circulating testosterone levels begins after puberty.⁸

Testosterone decline is associated with type II diabetes mellitus, dyslipidaemia, arterial hypertension, osteoporosis, muscle weakness, sexual dysfunction, depressed mood, etc. In general, testosterone decline increases the risk of all-cause and cardiovascular mortality.⁹ The main cause of testosterone decline is the disability of aged Leydig cells to produce testosterone in response to LH; there is no decline in number of Leydig cells or circulating LH levels with age. Testosterone decline is a result of complex functional changes in expression of steroidogenic enzymes, supply of cholesterol precursors to steroidogenic pathway, expression and function of mitochondrial cholesterol transport machinery (StAR protein and TSPO), expression of COX-2 gene which is inhibitor of StAR protein expression and Leydig cell steroidogenesis. Also, there are changes in cAMP signal which decline ability of Leydig cells to produce steroids and availability of testosterone precursor to steroidogenesis.⁸

Testosterone levels after prostate surgery

Surgical treatment of PC can influence the hypothalamic-pituitary-gonadal axis confirming the role of the prostate as an active endocrine organ. Radical prostatectomy (RP) increases testosterone and percent-free testosterone, estradiol, LH and follicle stimulating hormone (FSH) serum levels and decreases DHT serum level in one-year period.¹⁰

In comparison with external beam radiation therapy (EBRT) there is less impact on hypothalamic-pituitary-gonadal axis in patients treated surgically.¹¹

In patients with lower urinary tract symptoms (LUTS) treated with conservative therapy or transurethral resection of the prostate (TURP) there were no significant endocrine changes in 12 months period. Same study shows that baseline testosterone level is almost twice higher in the low-grade tumors group (Gleason score ≤ 6) than in the high-grade tumors group (Gleason score 7-10). Conversely, the results showed doubling of testosterone in 12-months-period in the high-grade tumors group in comparison to the low-grade tumors group.¹²

The influence of the testosterone in localized PC

Serum testosterone levels are associated with the prostate-specific antigen (PSA) levels, Gleason score and AR expression in newly diagnosed PC patients. In one retrospective study, men with low baseline testosterone level ($< 3,0$ ng/ml) had lower levels of LH, FSH and estradiol, PSA levels were lower, but mean Gleason score was higher. In these patients AR expression was higher in comparison to normal and high testosterone group.¹³

Another retrospective study of patients treated by RP showed connection between low baseline testosterone levels and increased body mass index and diabetes mellitus. More important, significantly lower testosterone levels were recorded in patients with lymph node metastases compared to patients with non-metastatic disease.¹⁴

In one large retrospective study, low baseline testosterone levels at diagnosis of PC were associated with aggressive type of PC and predicted poor PC-specific survival. Testosterone baseline levels significantly decreased as PC aggressiveness increased; the low testosterone group had 2,9-fold increased risk for intermediate-risk PC, 5,6-fold increased risk for high-risk PC, and 72,4-fold increased risk for metastatic PC compared with the normal testosterone group. Furthermore, the low testosterone group had 10,7-fold increased risk of the PC-specific mortality.¹⁵

There are data about patients with unfavorable-risk PC treated in prospective clinical trials with radiotherapy and ADT and their testosterone levels at the time of first PSA failure. Low (but not necessarily castration) testosterone levels at the time of first PSA failure confer a very poor prognosis, a significant increase in the risk of all-cause mortality and PC-specific mortality.¹⁶

Recent study from 2019 investigated the role of baseline free and total testosterone levels on post-operative oncologic outcomes, continence and erectile function. Low baseline free testosterone level was related to higher risk for pT3 PC and higher Gleason score; furthermore, it was an independent risk factor for biochemical recurrence in 52 months period. Baseline total testosterone level was related to pre-operative erectile dysfunction (ED) and baseline free testosterone level was related to post-operative ED in logistic regression.¹⁷

But some data are conflicting, and some results are opposite to those mentioned above. Result from the two large prospective cohort studies showed no significant association between quartile of total testosterone, sex hormone binding globulin (SHBG), SHBG-adjusted testosterone, free testosterone, DHT, androstenediol glucuronide or estradiol and lethal PC or total mortality. Also, there was no consistent association between lethal PC and sex hormone quartile in subset analyses stratified by Gleason score, TNM stage and age.¹⁸

Another study included two Phase III trials involving ADT and EBRT to assess the significance of a baseline testosterone levels. Results showed independent influence of age, Gleason score and PSA on an increased risk of biochemical relapse, metastatic disease and reduced cause-specific and overall survival. Baseline testosterone level doesn't affect these outcomes in patients treated with EBRT and ADT for PC.¹⁹

One collaborative analysis of 20 prospective studies showed that men with lowest free testosterone level had a lower risk of overall PC than men with higher concentration of free testosterone. Significant heterogeneity was present by tumor grade; very low free testosterone levels were associated with a lower risk of low- and intermediate-grade disease and a no significantly higher risk of high-grade disease.²⁰

The influence of testosterone in metastatic PC

As it is already mentioned, ADT plays a central role in PC treatment leading to beneficial responses in most patients with advanced disease, but some patients develop the castration-resistant disease as a result of AR amplification as the most important molecular alteration.⁴ One multicenter randomized phase III clinical trial (CALGB 9583) evaluated adrenal androgen

levels as predictors of outcome in PC patients treated with ketoconazole plus antiandrogen withdrawal. PSA response rate was almost 30% and median response duration was approximately 5 months. Univariate analysis showed that elevation of baseline androstenedione levels was predictive of PSA response. In multivariate analysis, in comparison to lower tertile baseline androstenedione levels, both the uppermost and the middle tertile of baseline androstenedione level were associated with an improved overall survival.²¹

Phase III study (COU-AA-301) showed that abiraterone acetate (AA) in combination with prednisone prolonged overall survival in patients with metastatic castration-resistant prostate cancer (mCRPC) after administration of docetaxel. In bivariate and multivariable analyses baseline androgen levels were strongly associated with survival. Baseline androgen levels above median compared with below median in both the AA+prednisone and prednisone group resulted with longer survival. Treatment with AA+prednisone resulted with longer survival versus prednisone alone in the above- or below-median group for all androgens.²²

In the next study, a prognostic and predictive value for survival and response to salvage hormonal therapy of baseline testosterone level was analyzed in mCRPC patients from nine different non-hormonal first-line chemotherapy phase II–III trials. Median overall survival was significantly longer if baseline testosterone level was above, rather than under the testosterone level median value. The presence of anemia in these patients was an unfavorable prognostic factor; the presence of low testosterone level and anemia had a worse outcome compared to those with one or none of them.²³

Large systematic review and meta-analysis in 2018 investigated 25 studies for the independent relationship between serum testosterone and prognosis of PC patients. The prognostic value of testosterone was evaluated in early-stage PC in 8 studies, in advanced PC before ADT in 4 studies, in advanced PC during ADT in 5 studies and in mCRPC in 8 studies. Serum testosterone level was not prognostic in terms of overall survival and biochemical recurrence in early-stage PC studies. In advanced PC studies, higher testosterone levels before ADT were associated with a reduced risk of death; but during ADT, lower testosterone levels were associated with a reduced risk of death and PC

progression. In mCRPC studies, higher testosterone levels predicted a reduced risk of PC progression, but not of death. The heterogeneity of the included studies was a major limitation of this meta-analysis. In conclusion, the relationship between serum testosterone and PC prognosis varies in different clinical settings and according to ADT administration.²⁴

Conclusions

Prostate cancer is known as an androgen-dependent tumor with testosterone as its natural growth factor, its action is mediated by the androgen receptor (AR) important for the biology and progression of PC. ADT plays the central role in PC treatment leading to beneficial responses in most patients with advanced disease. Some patients develop the castration-resistant disease as a result of AR amplification as the most important molecular alteration.⁴ Surgical treatment of PC can influence the hypothalamic-pituitary-gonadal axis with less impact on it compared to patients treated with radiation.^{10,11} RP increases testosterone and free testosterone, estradiol, LH and FSH serum levels and decreases DHT serum level in one-year period.¹⁰ In patients treated by RP, the baseline testosterone level is almost twice as higher in the low-grade tumors group than in the high-grade tumors group; there is also doubling of testosterone in 12-months period in the high-grade tumors group in comparison to the low-grade tumors group.¹² Patients with pre-operative low baseline testosterone level had mean Gleason score higher and AR expression was higher; significantly lower testosterone levels were recorded in patients with lymph node metastases.^{13,14} Low baseline testosterone level at diagnosis of PC is associated with aggressive type of PC and predicts poor PC-specific survival, the low testosterone group had 10,7-fold increased risk of the PC-specific mortality.¹⁵ Furthermore, low (but not necessarily castration) testosterone levels at the time of first PSA failure confer a very poor prognosis, a significant increase in the risk of all-cause mortality and PC-specific mortality.¹⁶ Still, some data are conflicting and some results are opposite to those mentioned before. These data showed that there is no significant association between all sex hormone in men and lethal PC or total mortality. There was no consistent association between lethal PC and sex hormone quartile in subset analyses stratified by Gleason

score, TNM stage and age.¹⁸⁻²⁰ In patients with metastatic PC, results showed that elevation of baseline androstenedione levels was predictive of PSA response; higher baseline androstenedione level were associated with an improved overall survival.²¹ In patients treated by AA+prednisone results showed longer survival in comparison to prednisone alone in the above- or below-median group for all androgens.²² In patients treated by non-hormonal first-line chemotherapy, median overall survival was significantly longer if baseline testosterone level was above than under the testosterone level median value.²³ Large systematic review and meta-analysis in 2018 showed that serum testosterone level was not prognostic in terms of overall survival and biochemical recurrence in early-stage PC studies. In advanced PC studies, higher testosterone levels before ADT were associated with a reduced risk of death; but during ADT, lower testosterone levels were associated with a reduced risk of death and PC progression. In mCRPC studies, higher testosterone levels predicted a reduced risk of PC progression, but not of death. The relationship between serum testosterone and PC prognosis varies in different clinical settings and according to ADT administration.²⁴ The association between serum testosterone levels and PC biology is complex and changes dynamically during the course of the disease. Still, some mechanisms of its interaction are unknown and deserve to be studied further.

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Sažetak

JE LI TESTOSTERON PROGNOŠTIČKI VAŽAN U LIJEČENJU RAKA PROSTATE. UROLOŠKO STAJALIŠTE.

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Karcinom prostate (KP) je androgen-ovisan tumor kojem je testosteron prirodni faktor rasta, njegovo djelovanje je posredovano putem androgenih receptora (AR) važnih za biologiju i progresiju KP. Tijekom starenja započinje progresivni pad serumske razine testosterona uzrokovan nesposobnošću ostarjelih Leydigovih stanica za stvaranje testosterona kao odgovor na stimulaciju luteinizirajućeg hormona. Kirurško liječenje KP može utjecati na os hipotalamus-hipofiza-gonade, ali s manjim utjecajem u usporedbi s pacijentima liječenim radioterapijom. Kod pacijenata s nižim preoperativnim razinama testosterona bilježe se povišene srednje vrijednosti Gleason zbroja i pojačana ekspresija AR; značajno niže razine testosterona zabilježene su kod pacijenata s metastazama u limfnim čvorovima. Ipak, neki podaci su kontradiktorni i u suprotnosti s prethodno navedenim. Ovi podaci pokazuju da ne postoji značajna povezanost između spolnih hormona u muškaraca i letalnog KP te ukupnog mortaliteta. Kod pacijenata s metastatskim KP, elevacija početnih razina androstendiona se pokazala prediktivnom u odgovoru prostata-specifičnog antigena (PSA) i poboljšanju općeg preživljenja. Kod tih pacijenata, odnos između serumskih razina testosterona i prognoze KP varira u različitim kliničkim okolnostima i ovisno o aplikaciji androgen deprivacijske terapije.

Ključne riječi: *rak prostate, androgen deprivacijska terapija, metastatski karcinom prostate, testosteron u serumu*