Objective: To estimate the value of urinary prostate specific antigen (uPSA) determination in the monitoring of prostate cancer (PCa) patients. Material and methods: From January 2001 to December 2011, uPSA was determined in 397 patients. There were 265 patients with benign prostate, 19 with prostatitis and 113 with prostate cancer. Radical retropubic prostatectomy (RRP) was performed at 65 patients, while 48 patients had PCa re-ceived antiandrogen therapy. Results: Average uPSA value in the patients with benign prostate hyperplasia (BPH) was 190.8 ± 184.2 ng/mL. Average uPSA in the patients with PCa was 287.5 ± 303.4 ng/mL and it was not significantly different from BPH group. The average uPSA in the prostatitis group was 113.1 ± 148.5 ng/mL, and 16.4 ± 36.7 ng/mL in the post RRP group. During antiandrogen therapy, uPSA and PSA correlated significantly (r=0.49). Conclusion: The uPSA level reflects the response of normal prostatic and urethral secretory cells on total androgen activity. The uPSA level cannot distinguish the cases with BPH and cases with PCa. In addition, in the patients after RRP, uPSA reflects local urethral PSA production and has no role in the diagnosis of PCa recurrence. However, uPSA is better indicator of androgen suppression than testosterone (T), as it reflects the effect of suppression of all androgens, not only T.

Key words: benign prostatic hyperplasia, prostate specific antigen, urinary prostate specific antigen, prostate cancer, antiandrogen therapy

INTRODUCTION

The embryonal development of the prostate, as well as prostatic growth and the development of benign prostatic hyperplasia (BPH) and prostate cancer (PCa) are all influenced by androgens. The main serum androgen in the male is testosterone (T), secreted from the testis, while dihydrotestosterone (DHT) is the most important and the most potent intraprostatic androgen. Enzymes 5 alpha-reductase (5AR), type 1 and 2, convert T to DHT; 5AR-2 is the predominant isozyme expressed in the stromal cells. However, adrenal androgens, mainly dehydroepiandrosterone (DHEA), can also be converted into T and DHT in the prostatic cells. The contribution of adrenal androgens in the synthesis of prostatic androgens is very high: after castration, serum T concentration is reduced by 97%, while the sum of androgen metabolites is reduced by 59%. That means that 41% of androgens are present in the prostate after castration. Other studies confirmed that intraprostatic DHT concentration after castration falls on 39%- 50% of the pre-treatment level. These studies confirmed the significance of total androgen blockade (TAB) in the treatment of advanced PCa, but they also confirmed that the measurement of serum T cannot be a measure of the total androgenic activity in the circulation.

Prostate specific antigen (PSA) is the most important tool in the assessment of the response on the antiandrogen therapy in the PCa patients. The synthesis of PSA depends on sum of all serum androgens and intraprostatic T and DHT. In the genomic process, T and DHT molecules bind to androgen receptor (AR), enter the nucleus and together with AR bind to specific DNA sequences, where they stimulate genes responsible for cell growth and PSA synthesis. The other possible pathway of PSA synthesis is via specific cell-membrane steroid receptor. The concentration of PSA in prostatic tissue is higher in BPH than in normal prostate and low in malignant cells. The synthesis of PSA takes place in the secretory cells. After the synthesis, PSA molecules are contained in so-called prostatic secretory granules (PSG), in the cytosol. In the process of “apocrine decapitation”, PSGs are thrown out in the prostatic ducts, where PSA molecules
are released. Contained in the seminal fluid, PSA molecules leak to the prostatic urethra, and collect till the next micturition, when they are expelled from the body.

Additional PSA molecules are secreted from urethral secretory cells, so-called "minor prostatic glands". There are no PSA molecules in the upper urinary tract. Average uPSA concentration in the patients with BPH is roughly 200 ng/ml and it cannot differentiate the patients with BPH and PCa. In addition, uPSA cannot indicate the recurrence after radical prostatectomy, because the main source of PSA molecules after RP is the urethra.

MATERIAL AND METHODS

From January 2001 to December 2011, uPSA was determined in 397 patients. There were 265 patients with benign prostate, 19 with prostatitis and 113 with prostate cancer. Radical retropubic prostatectomy (RRP) was performed at 65 patients, while 48 patients had PCa received antiandrogen therapy (AAT). The patients with prostatitis underwent TRUS-guided biopsy due to elevated PSA. The determinations of serum and urinary PSA were done in the Central laboratory of Clinical Centre of Serbia, using AxSYM Total PSA assay (Abbott Laboratories, Illinois, USA) till September 2009. From September 2009, ARCHITECT Total PSA assay (Abbott Laboratories, Illinois, USA) was used.

RESULTS

Average uPSA value in the patients with benign prostate hyperplasia (BPH) was 190.8±184.2 ng/mL (range 1.8 - 870.5 ng/mL). Average uPSA in the patients with PCa was higher than in the BPH group (287.5±303.4 ng/mL), but it was not significantly different (p=0.016). Average uPSA in the prostatitis group was 113.1±148.5 ng/mL, while uPSA in the RRP was 16.4±36.7 ng/mL (Table 1). During AAT, uPSA and PSA correlated significantly (r=0.49).

DISCUSSION

Serum PSA is the best monitor of PCa response during antiandrogen therapy. However, in hormone-refractory prostate cancer (HRPCa), PSA continues to rise despite TAB. This phenomenon can be explained with changes of AR in malignant cells (elevated levels of AR, or AR modifications that modify the response of antiandrogens) and with local intraprostatic synthesis of androgens. From the other hand, there are no changes of AR in normal prostatic cells and they probably minimize, or discontinue PSA synthesis during therapy. Being the product of normal secretory cells of the prostate and urethra, uPSA can serve as a control of antiandrogen effect.

In the patients with PCa who receive antiandrogen therapy, parallel monitoring of PSA and uPSA is superior to monitoring of PSA and T. To be precise, serum T represents only testicular androgen production, while uPSA reflects total androgenic activity.
EXAMPLES

Example 1. Patient M. N, 71 years old, with PCa in stage T2b, who refused curative treatment. The patient accepted monotherapy with nonsteroidal antiandrogen. Almost parallel decrease of PSA and uPSA during antiandrogen therapy means that the majority of PCa clones react similarly like normal secretory cells (Figure 3).

Example 2. Patient Z. D, 75 years old, with T2c stage PCa. He had chronic cardiomyopathy and obesity and refused radiation therapy. After introducing reduced dose of steroid antiandrogen, both PSA and uPSA dropped rapidly. During the next 12 months, patient underwent mild antiandrogen suppression with finasteride, meanwhile PSA and uPSA slowly increased. Finally, the combination of reduced dose of steroid antiandrogen and finasteride resulted in significant suppression of PSA synthesis in both malignant and normal cells (Figure 4).

Example 3. Patient R. D, 67 years old, with stage T3 PCA. The patient underwent radiation therapy and was in remission for one year, when PSA rised to 22 ng/mL and steroid antiandrogen was introduced. Due to constant PSA rise, nonsteroidal antiandrogen was introduced. PSA continued to rise and bone scan revealed osseous metastases. During LH-RH analogue and TAB (LH-RH analogue + nonsteroidal antiandrogen), PSA continued to rise, while uPSA dropped to low level, of 0.12- 0.31 ng/mL. In this case, the divergence of PSA and uPSA curves indicated the development of HRPCa (Figure 5).

CONCLUSION

The uPSA level reflects the response of normal prostatic and urethral secretory cells on total androgen activity. The level of uPSA cannot distinguish the cases with BPH and cases with PCa. In addition, in the patients after RRP, uPSA reflects local urethral PSA production and has no role in the diagnosis of PCa recurrence.

However, during antiandrogen therapy of PCa, uPSA is better indicator of androgen suppression than T, as it reflects the effect of suppression of total androgen pool. Moreover, simultaneous monitoring of PSA and uPSA in patients with PCa offers valuable information about prognosis of these patients.

SUMMARY

URINARNI PSA U PRAČENJU REZULTATA LEČENJA BOLESNIKA SA KARCINOMOM PROSTATE

Cilj rada: Ispitati vrednost urinarnog prostata specifičnog antigena (uPSA) u pračenju rezultata lečenja karcinoma prostate


Rezultati: prosečna vrednost uPSA kod bolesnika sa BHP je bila 190.8±184.2 ng/mL, a kod bolesnika sa karcinomom prostate 287.5±303.4 ng/mL. Prosečna vrednost uPSA kod bolesnika sa prostatitisom je bila 113.1± 148.5 ng/mL, a kod bolesnika sa učinjenom RRP, 16.4±36.7 ng/mL. Tokom antiandrogene terapije, postojala je dobra korelacija između uPSA i PSA (r=0.49).

Zaključak: Nivo uPSA odražava odgovor normalnih sektornih celija prostate i uretre na ukupnu androgenu aktivnost. Pomoću nivoa uPSA nije moguće razlikovati bolesnike sa BHP i karcinomom prostate. Pored toga, kod bolesnika sa učinjenom RRP, uPSA je rezultat lokalne uretralne proizvodnje PSA i zato ne može da bude pokazatelj lokalnog recidiva. Ipak, tokom antiandrogene terapije karcinoma prostate, uPSA je bolji pokazatelj ukupne androgene supresije nego testosteron.

Ključne reči: benigna hiperplazija prostate, prostata specifični antigen, urinarni prostata specifični antigen, karcinom prostate, antiandrogena terapija.
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