新潟県厚生連医誌　第9巻　1号　22～27　1999

Original Article

The ratio of serum gamma-seminoprotein to total prostate specific antigen during hormonal therapy for prostate cancer

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Background: Prostate cancer patients have a lower ratio of free to total prostate specific antigen (tPSA) compared to patients with benign prostatic hyperplasia. Anti-gamma-seminoprotein (γ-Sm) antibody identifies free PSA exclusively. We analyzed changes in the ratio of γ-Sm to tPSA during hormonal therapy.

Patients and Methods: Forty-five patients were newly diagnosed with prostate cancer. Fifteen patients were treated during relapse with hormonal therapy.

Results: There was no difference between γ-Sm/tPSA ratios in patients with localized cancer and those with metastatic cancer at diagnosis. The γ-Sm/tPSA ratio of the patients with localized cancer who were treated with surgical castration was elevated significantly 2 weeks after treatment ($p=0.0049$), but this ratio was not different in patients with metastatic cancer ($p=0.13$). The γ-Sm/tPSA ratio in patients with localized cancer who were treated with LH-RH agonist did not elevate significantly ($p=0.11$), but the ratio decreased significantly with metastatic cancer ($p=0.023$). The ratio at the time of relapse with hormonal therapy decreased significantly ($p=0.0023$).

Conclusions: Shifts in the γ-Sm/tPSA ratio may predict whether prostate cancer will respond to hormonal therapy.

Key words: prostate carcinoma, prostate-specific antigen, gamma-seminoprotein, hormonal therapy

INTRODUCTION

Serum prostate specific antigen (PSA) exists in different forms.[1,2] PSA is predominantly bound to α1-antichymotripsin (PSA-ACT) accounting for 70 to 90% of total PSA (tPSA). Approximately 10 to 30% of tPSA is not bound to proteins and is called free PSA (fPSA). In Japan, another tumor marker, gamma-seminoprotein (γ-Sm), has been used to detect prostate cancer. Recently, the amino acid sequence for γ-Sm was found to be identical to PSA.[3] Anti-γ-Sm antibody identifies free PSA exclusively. The ratio of fPSA to tPSA has been reported to be influenced by prostate volume, tumor TNM stage, and grade.[4-8] In the current study, we analyzed changes in the ratio of γ-Sm to tPSA during hormonal therapy.

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MATERIALS AND METHODS

Patients

Between September 1995 and February 1997, 45 patients aged 48 to 97 (average 73) were newly diagnosed with prostate cancer. A clinical stage and pathologic grade were assigned to each patient according to the system determined by the Japanese Urological Association and the Japanese Pathological Society.[9] Twenty-one patients were diagnosed with localized cancer (stage B or C,). Twenty-four had metastatic cancer (stage D1 or D2). Blood

sampling for tPSA and γ-Sm was performed prior to and 2 weeks after hormonal therapy. Of the 45 patients, 34 were treated with surgical castration and 11 luteinizing hormone-releasing hormone (LH-RH) agonists. Thirty-seven patients received flutamide, six received chlormadinone acetate, and two received estramustine phosphate.

Patients were diagnosed with relapsed disease when the serum tPSA level was elevated at two serial points. Fifteen patients were treated during relapse with hormonal therapy, 11 were treated with surgical castration, and four received luteinizing hormone-releasing hormone (LH-RH) agonists. Five patients were treated with flutamide, three with chlormadinone acetate, and five with estramustine phosphate.

Methods

A two-site immunoenzymometric assay using the Tosoh PSA kit reagent (AIA-PACK PA) (Tosoh Co., Tokyo, Japan) was used to measure tPSA concentrations in serum, This kit can detect both PSA-ACT and fPSA, or tPSA. γ-Sm concentrations in serum were measured with the Chugai γ-Sm kit (Chugai Pharmaceutical Co., Tokyo, Japan).

Table 1. Serum PSA and γ-Sm levels in newly diagnosed patients (±standard deviation)

	tPSA (ng/ml)	γ-Sm (ng/ml)	γ-Sm/tPSA
patients with localized cancer (n=21)	72.4±63.7	19.0±20.7	0.285±0.160
patients with metastatic cancer (n=24)	1380.9±1656.1	130.7±227.6	0.293±0.205

Table 2. Serum PSA and γ-Sm levels in newly diagnosed patients treated with surgical castration (±standard deviation)

	Pre PSA (ng/ml)	Pre γ-Sm (ng/ml)	Pre γ-Sm/PSA	Post PSA (ng/ml)	Post γ-Sm (ng/ml)	Post γ-Sm/PSA
patients with localized cancer (n=14)	78.8±71.1*1	19.9±21.9*2	0.288±0.177*3	14.1±15.1*1	5.3±4.3*2	0.746±0.542*3
w+m (n=10)	72.8±71.7*4	18.9±24.2*5	0.300±0.207*6	13.1±16.8*4	5.3±4.7*5	0.901±0.570*6
p (n=4)	93.8±78.0*7	22.5±17.6*8	0.259±0.0800*9	16.7±11.6*7	5.4±3.5*8	0.360±0.135*9
patients with metastatic cancer (n=20)	1584.9±1741.3*1	263.6±235.5*2	0.282±0.200*3	337.7±606.7*1	111.2±211.1*2	0.376±0.411*3
w+m (n=13)	1924.7±1816.4*4	284.3±264.7*5	0.229±0.190*6	258.8±189.7*4	105.2±218.6*5	0.367±0.481*6
p (n=6)	1030.5±1642.2*7	224.3±198.6*8	0.366±0.206*9	546.5±1110.6*7	133.4±231.2*8	0.374±0.474*9

*1 p=0.00089	*4 p=0.0073	*7 p=0.053
*2 p=0.0097	*5 p=0.047	*8 p=0.052
*3 p=0.0049	*6 p=0.0066	*9 p=0.036
*1 p=0.00074	*4 p=0.0021	*7 p=0.039
*2 p=0.0054	*5 p=0.023	*8 p=0.046
*3 p=0.13	*63 p=0.12	*9 p=0.47

Pre: prior to hormonal therapy
Post: two weeks after hormonal therapy
w: well differentiated adenocarcinoma
m: moderately differentiated adenocarcinoma
p: poorly differentiated adenocarcinoma

Statistical Analysis

Student's t test was used for comparison of serum tPSA levels, γ-Sm levels, and γ-Sm/tPSA ratios with P values <0.05 considered as significant.

RESULTS

Serum tPSA and γ-Sm levels in newly diagnosed patients

Table 1 shows serum tPSA and γ-Sm levels in newly diagnosed patients. Although tPSA and γ-Sm levels in patients with metastatic cancer were higher than in patients with localized cancer, there was no difference in γ-Sm/tPSA ratio between patients with localized cancer and those with metastatic cancer.

Serum tPSA and γ-Sm levels in newly diagnosed patients after surgical castration

Table 2 shows serum tPSA and γ-Sm levels in newly diagnosed patients treated with surgical castration (n=27). tPSA and γ-Sm levels in patients with localized or metastatic cancer decreased significantly after treatment (p=0.0008 and P=0.0038, respectively). γ-Sm/tPSA ratios in patients with localized cancer (n=14) were elevated significantly 2 weeks after treatment (p=0.0049). However, this ratio in patients with metastatic cancer (n=13) was not increased significantly 2 weeks after treatment (p=0.13).

Serum tPSA and γ-Sm levels in newly diagnosed patients treated with LH-RH agonist

Table 3. Serum PSA and γ-Sm levels in newly diagnosed patients treated with LH-RH agonist (±standard deviation)

	Pre tPSA (ng/ml)	Pre γ-Sm (ng/ml)	Pre γ-Sm/tPSA	Post tPSA (ng/ml)	Post γ-Sm (ng/ml)	Post γ-Sm/tPSA
patients with localized cancer (n=7)	59.7±47.8*1	17.3±19.3*2	0.278±0.131*3	23.1±16.9*1	6.1±3.9*2	0.478±0.396*3
patients with metastatic cancer (n=4)	360.5±397.8#1	66.0±49.3#2	0.349±0.253#3	29.8±28.5#1	4.8±3.1#2	0.263±0.204#3

*1 p=0.015
*2 p=0.081
*3 p=0.11

#1 p=0.086
#2 p=0.039
#3 p=0.023

Pre: prior to hormonal therapy
Post: two weeks after hormonal therapy

Table 4. Serum PSA and γ-Sm levels in patients in relapse after hormonal therapy (±standard deviation)

	Pre tPSA (ng/ml)	Pre γ-Sm (ng/ml)	Pre γ-Sm/tPSA	Post tPSA (ng/ml)	Post γ-Sm (ng/ml)	Post γ-Sm/tPSA
patients in relapse with hormonal therapy (n=15)	13.3±17.5*1	9.6±13.2*2	0.696±0.393*3	32.9±41.2*1	17.9±26.7*2	0.446±0.236*3

*1 p=0.010
*2 p=0.032
*3 p=0.0023

Pre: nadir of tPSA
Post: at diagnosis of relapse

Table 3 shows serum tPSA and γ-Sm levels in patients treated with LH-RH agonist (n=11). tPSA and γ-Sm levels decreased significantly with treatment (p=0.044 and P=0.015, respecti vely). The γ-Sm/tPSA ratio in patients with localized cancer (n=7) did not change significantly 2 weeks after the treatment (p=0.11). However, the ratio in patients with metastatic cancer (n=4) decreased significantly 2 weeks after the treatment (p=0.023).

Serum tPSA and γ-Sm levels in relapsed patients after hormonal therapy

Table 4 shows tPSA and γ-Sm levels in relapsed patients (n=15). Both tPSA and γ-Sm levels showed serial increases at the time of relapse (p=0.01 and P=0.032, respectively). γ-Sm/tPSA ratio decreased significantly (p=0.0023).

DISCUSSION

Serum PSA levels are extremely useful in the follow-up of patients undergoing hormonal therapy for prostate cancer.[10),11)] Although widely accepted as a marker for measuring response to treatment in prostate cancer patients on hormonal therapy, there is no consensus on which PSA parameter to follow. Commonly reported parameters include pretreatment PSA, the post-treatment nadir, the rate of PSA decrease, and the percentage serum PSA decrease.[10),11)]

Part of PSA binds to proteins in the blood and some PSA remains free or unbound.[1),2)] Recent publications have reported on the use of molecular forms to distinguish between patients with prostate cancer and those with benign prostatic hyperplasia.[1),2),12)] Prostate cancer patients have lower ratios of fPSA to tPSA than the patients with benign prostatic hyperplasia. We now believe that anti-γ-Sm antibody recognizes uncomplexed fPSA.[3),4),12)]

In our study, the γ-Sm/tPSA ratio in patients with localized cancer elevated significantly 2 weeks after treatment. However, the ratio in patients with metastatic cancer did not change significantly after treatment. The γ-Sm/tPSA ratio at relapse was noted to decrease significantly. Indeed, compared with tPSA, the free-to-total PSA ratio is of no additional value in the clinical staging of prostate cancer, however, the ratio of free to total PSA may predict at the time of diagnosis whether prostate cancer will be an aggressive or a more indolent cancer.[7),8)] In our study, the change in the γ-Sm/tPSA ratio, or the free-to-total PSA ratio may predict whether prostate cancer will respond to hormonal therapy.

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原　著

前立腺癌治療に伴うγSm/PSAの変化

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【背景】前立腺癌(CAP)治療に伴う前立腺特異抗原(PSA)の変化の観察は重要である。非結合型PSA比率がCAP早期発見に有用であるとの報告が散見される。γSmは非結合型PSAを測定しているとされる。【方法】CAPの内分泌療法に伴うPSAの変化をγSm/PSA比率で検討した。【結果】治療開始症例では治療開始前と2週間後で比較すると、限局癌症例で有為にγSm/PSA比率の上昇を認めた。転移症例は限局癌症例に比較してその上昇は軽度であった。組織分化度が高いほどその上昇は高度であった。抗アンドロゲン除去症候群発現症例でもPSA低下に伴ってγSm/PSA比率の上昇を認めたが、デキサメサゾン有効症例では一定の傾向を認めなかった。再燃症例ではPSA上昇に伴ってγSm/PSA比率の低下を認めた。【結語】治療に伴うγSm/PSA比率の変化はCAPの治療に対する反応性の指標になりうると考えられた。

キーワード：前立腺癌，前立腺特異抗原，γセミノプロテイン，ホルモン療法

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