The Pattern of Prostate-Specific Antigen Responses Following Hormonal Therapy in Thai Men with Bone Metastatic Prostate Cancer

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Abstract

Objective : To study the pattern of prostate-specific antigen (PSA) responses and prognostic factors following hormonal therapy in Thai men with bone metastatic prostate cancer.

Material and Method : Forty-four patients with bone metastatic prostate cancer treated by bilateral orchiectomy were retrospectively studied for PSA responses during follow-up. The endpoint was time to PSA biochemical failure. PSA pattern and the prognostic factors were evaluated.

Results : PSA levels regressed to PSA nadir level in all patients. Time to 50 per cent PSA regression, time to PSA nadir level and time to biochemical failure were 2.1, 6.7 and 11.2 months, respectively. While biochemical failure was present, all patients were alive and had stable clinical conditions. Tumor grading was an important prognostic factor while age and pretreatment PSA level were not a significant indicator. Times to biochemical failure in the patients with well, moderate and poor differentiated tumors were 19.3, 10.0 and 9.3 months, respectively.

Conclusion : Following bilateral orchiectomy in Thai men with bone metastatic prostate cancer, PSA level decreased continuously to the PSA nadir level in 6-7 months and stable for a period then it increased, known as biochemical failure. The patients with a well differentiated tumor had a significantly longer time to biochemical failure when compared to the patients with a moderate or poor differentiated tumor.

Key word : Prostate-Specific Antigen, Prostate, Prostatic Carcinoma

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Apparently, prostate-specific antigen (PSA) is used to monitor the outcomes of prostate cancer therapies[1-3]. Usually, PSA would decrease if the disease was regressive. PSA may reach the undetectable level in patients who achieve the curable status. The lower the PSA level, the better the prognosis. On the other hand, PSA continuously increases in cases of tumor progression. PSA is the most sensitive parameter to detect recurrence or progression of disease known as biochemical progression or biochemical failure[2,4]. The longer time to biochemical failure, the better the result of therapy. However, the outcomes of therapies for metastatic prostate cancers are varied among patients who have different bio-characteristics such as age, tumor grading or pretreatment PSA level. To study the pattern of PSA responses and prognostic factors after hormonal therapy of bone metastatic prostate cancer in Thai men, this descriptive study was conducted.

MATERIAL AND METHOD

From January 1998 to February 2002, Thai patients with bone metastatic prostate cancer were studied. Patients lost to follow-up or who had incomplete data were excluded. Forty-four patients were included in the study. All patients were diagnosed by transrectal ultrasound guide biopsy (TRUSbx) or transurethral prostatectomy (TURP). Tumor grading was classified as well differentiated tumor (Gleason score 2-4), moderate differentiated tumor (Gleason score 5-7) or poor differentiated tumor (Gleason score 8-10). Bone scans showed metastasis (stage D2) at the first diagnosis in all patients. Bilateral orchiectomy was treated as hormonal therapy in all patients. PSA was tested at the first diagnosis and then was used to monitor disease every 1 to 3 months after bilateral orchiectomy. The end point of this study was the time of PSA progression from the PSA nadir level following bilateral orchiectomy known as time to biochemical failure. Patterns of PSA level responses were evaluated. Age, tumor grading, pretreatment PSA level were analyzed with the time to biochemical failure. Descriptive analysis was used for bio-characteristic evaluation of the patients. *T*-test and ANOVA test were used to calculate correlation and regression of PSA level to time to biochemical failure. All statistic analysis was calculated by SPSS program.

RESULTS

Mean age was 70.4 years (range 55 to 86 years). Table 1 shows the characteristics of age, symptoms, tumor grading, and diagnostic methods. After bilateral orchiectomy, the patients were followed-up with PSA testing. Follow-up periods were 3 to 31 months. PSA level regressed to the PSA nadir level in all patients. However, biochemical failure was also detected after PSA reached the nadir level in all patients. Table 2 shows means, medians and ranges of pretreatment PSA level, PSA nadir level, time to PSA nadir and time to biochemical failure. The pattern of PSA regression calculated between the mean of PSA regression and duration of follow-up following bilateral orchiectomy is shown in Fig. 1. The data from Table 2 and Fig. 1 shows that time to 50 per cent PSA regression, time to PSA nadir level and time to biochemical failure were 2.1, 6.7 and 11.2 months, respectively. However, PSA levels were stable at PSA nadir level at almost 5 months. Interestingly, all patients were alive and had stable clinical conditions while biochemical failure was presenting.

Table 1. Characteristics of all patients.

Characteristics	Number of patients	%
Age group		
Less than 70 years	20	45.5
70 years or above	24	54.5
Symptoms		
LUTS	17	38.6
Urinary retention	19	43.2
Bone Pain	6	13.6
Fracture spine and paralysis	2	4.5
Tumor grading		
Well differentiation	7	15.9
Moderate differentiation	21	47.7
Poor differentiation	16	36.4
Diagnostic methods		
TRUS with biopsy	24	54.5
TURP	20	45.5

LUTS = Lower urinary tract symptoms

To evaluate the prognostic factors of biochemical failure in bone metastatic prostate cancer, parameters such as age group, pretreatment PSA level and tumor grading were analyzed with time to biochemical failure. The patients were divided into 2 age groups with the cut off point of 70 years old as shown in Table 3. No statistically significant difference of time to biochemical failure was found between the 2 groups (p-value = 0.85). Pretreatment PSA was analyzed with time to biochemical failure. Since the distribution of pretreatment PSA level was not a normal curve, log 10 pretreatment PSA level was analyzed. Mean log 10 pretreatment PSA level was 2.63. Log

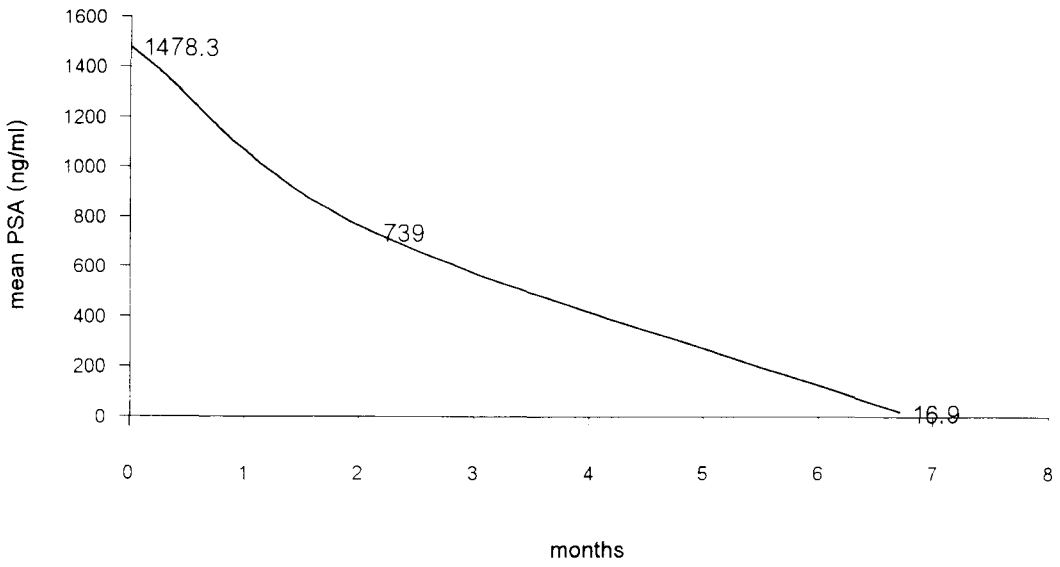

Fig. 1. Mean PSA regression after bilateral orchiectomy.

Table 2. Means, medians and ranges of pretreatment PSA level, PSA nadir level, time to PSA nadir level and time to biochemical failure in all patients.

PSA parameters	Mean	Median	Range
Pretreatment PSA level (ng/ml)	1,478.3 (SD 3079.2)	423.0	3.4-14400.0
PSA nadir level (ng/ml)	16.9 (SD 29.5)	3.2	0.0-125.0
Time to PSA nadir (months)	6.7 (SD 4.9)	6	1-24
Time to biochemical failure (months)	11.2 (SD 5.6)	10	3-31

10 PSA 2.63 was PSA level of 398 ng/ml. Patients were divided into 2 groups by the mean of log 10 pretreatment PSA level of 2.63. Group 1 was the patients with log 10 pretreatment PSA less than 2.63 while group 2 was the patients with log 10 pretreatment PSA level 2.63 or above as shown in Table 4. No statistically significant difference was found between the 2 groups (p-value = 0.81). Tumor grading was also analyzed to time to biochemical failure. The patients were divided into 3 groups by tumor grading of well differentiation (Gleason score 2-4), moderate differentiation (Gleason score 5-7) or poor differentiation (Gleason score 8-10). Table 5 shows means, ranges and 95 per cent confidence intervals of time to biochemical failure among the 3 groups. The present data suggested that time to biochemical failure of the patients with a well differentiated tumor was significantly longer than the patients with a moderate or poor differentiated tumor with p-value of 0.02 and 0.01, respectively. However, times to biochemical failure of the patients with a moderate and poor differentiated tumor were not significantly different (p-value = 0.51) as shown in Fig. 2. The present data suggested that age and pretreatment PSA level were not a prognostic indicator while tumor grading was a significant prognostic factor. A well differentiated tumor (Gleason score 2-4) had good prognosis.

DISCUSSION

It is known that hormonal therapy has been widely used to treat bone metastatic prostate cancer. However, it is palliative. A tumor would be subse-

Table 3. Time to biochemical failure in different age groups.

Age groups	Number	Mean time to biochemical failure (months)
Less than 70 years old	20	10.6 (SD = 5.1)
70 years old or above	24	11.7 (SD = 6.0)

Table 4. Time to biochemical failure in different groups of log 10 pretreatment PSA.

Log 10 pretreatment PSA	Number	Mean time to biochemical failure (months)
Less than 2.63	22	11.8 (SD = 6.2)
2.63 or above	22	10.7 (SD = 5.1)

Log 10 pretreatment PSA 2.63 = PSA level of 398 ng/ml

Table 5. Means, ranges and 95 per cent confidence intervals of time to biochemical failure in patients with different tumor grading.

Tumor grading	Number	Time to biochemical failure (months)		
		Mean	Range	95% confidence interval
Well differentiation	7	19.3 (SD = 7.4)	11-31	12.5-26.1
Moderate differentiation	21	10.0 (SD = 4.3)	3-19	8.0-12.0
Poor differentiation	16	9.3 (SD = 2.5)	5-13	7.9-10.6

quently progressive known as hormonal refractory prostate cancer. PSA has been used to evaluate tumor regression or progression during follow-up. Prostate cancer has various spectrums among different races and environments[5,6]. The present data shows the pattern of PSA responses in Thai men with bone metastatic prostate cancer. PSA was continuously regressive to the nadir level approximately in 6 to 7 months. The PSA nadir level is very low when compared to the pretreatment PSA level in terms of both mean and median. Interestingly, PSA in some patients reached the undetectable level despite the patients having multiple bone metastasis or a complete hard prostate gland. Unfortunately, PSA nadir level was temporary. PSA would rise approximately 5 months after the nadir level. Progression of the PSA level presented in all patients even in those with a PSA nadir level of 0.0 ng/ml. This suggest that biochemical failure is present in all bone metastatic prostate cancer. In addition, PSA nadir at the undetectable level in metastatic prostate cancer could not indicate that the patients were safe from prostate cancer. Thus, the pattern of changing of PSA level is more important than any single value of PSA testing. Importantly, clinical statuses of all patients are still stable while biochemical failure is presenting. The present data showed that biochemical failure occurs earlier than clinical progression such as progressive bone pain, pathological bone fracture or progressive obstructive uropathy. Some data from western countries also showed a significant correlation between PSA response and progression or survival after hormonal therapies in metastatic prostate cancer[7,8]. To early detect tumor progression, the authors recommend that PSA monitoring is an important parameter. PSA testing should be tested continuously at least every 3 months after hormonal therapy.

Prognostic factors are usually evaluated at the time of diagnosis. For patients with no metastasis, pretreatment PSA level, pathological staging and tumor grading are the significant prognostic factors [9]. For patients with bone metastatic prostate cancer,

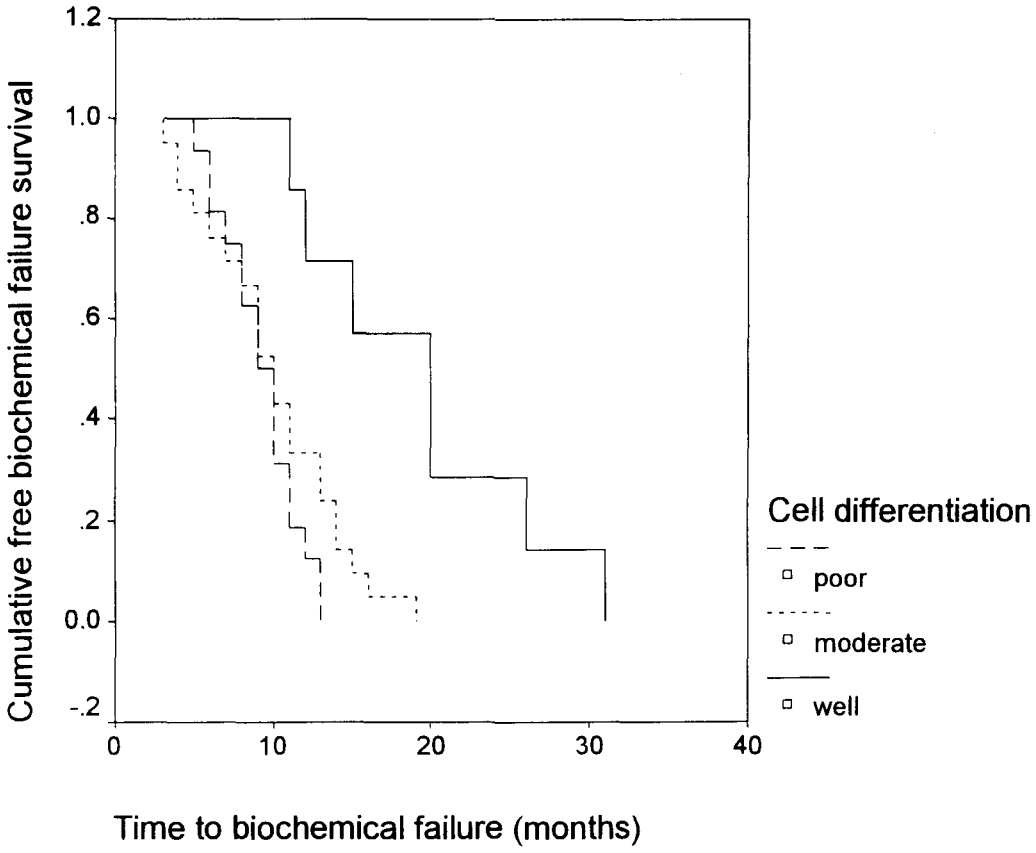

Fig. 2. Kaplan-Meier Curve of time to biochemical failure in patients with different tumor grading.

the authors evaluated prognostic factors in Thai men with age, pretreatment PSA level and tumor grading. The presented data shows that only the grading system is an important prognostic indicator while age and pretreatment PSA level are not. Patients with low grade tumor or Gleason score 2-4 had a good prognosis even though pretreatment PSA was high. Time to biochemical failure was almost 20 months. In addition, the patients had no clinical progression at the time of biochemical failure. When biochemical failure was detected, further management would be applied before clinical progression which may improve the quality of life or possible survival.

SUMMARY

The pattern of PSA response following bilateral orchiectomy in Thai men with bone metastasis is that the PSA level would decrease continuously to the PSA nadir level in 6-7 months and be stable for a period, then it would increase known as biochemical failure. Biochemical failure presented while there was no evidence of clinical progression. The patients with a well differentiated tumor had a better prognosis compared to the patients with moderate or poor differentiated tumor in terms of time to biochemical failure. Pretreatment PSA level and age are not the prognostic indicators.

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REFERENCES

1. Reynard JM, Peters TJ, Gillatt D. Prostate-specific antigen and prognosis in patients with metastatic prostate cancer -- a multivariable analysis of prostate cancer mortality. Br J Urol 1995; 75: 507-15.
2. Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. JAMA 1999; 281: 1591-7.
3. Oosterlinck W, Mattelaer J, Casselman J, Van Velthoven R, Derde MP, Kaufman L. PSA evolution: A prognostic factor during treatment of advanced prostatic carcinoma with total androgen blockade. Data from a Belgian multicentric study of 546 patients. Acta Urol Belg 1997; 65: 63-71.
4. Borghede G, Aldenborg F, Wurzinger E, Johansson KA, Hedelin H. Analysis of the local control in lymph-node staged localized prostate cancer treated by external beam radiotherapy, assessed by digital rectal examination, serum prostate-specific antigen and biopsy. Br J Urol 1997; 80: 247-55.
5. Shimizu H, Ross RK, Bernstein L, Yatani R, Henderson BE, Mack TM. Cancers of the prostate and breast among Japanese and white immigrants in Los Angeles County. Br J Cancer 1991; 63: 963-6.
6. Landis SH, Murray T, Bolden S, Wingo PA. Cancer statistics, 1999. CA Cancer J Clin 1999; 49: 8-31.
7. Cooper EH, Armitage TG, Robinson MR, et al. Prostatic specific antigen and the prediction of prognosis in metastatic prostatic cancer. Cancer 1990; 66 (Suppl): 1025-8.
8. Dijkman GA, Janknegt RA, De Reijke TM, Debruyne FM. Long-term efficacy and safety of nilutamide plus castration in advanced prostate cancer, and the significance of early prostate specific antigen normalization. International Anandron Study Group. J Urol 1997; 158: 160-3.
9. Hull GW, Rabbani F, Abbas F, Wheeler TM, Kattan MW, Scardino PT. Cancer control with radical prostatectomy alone in 1,000 consecutive patients. J Urol 2002; 167: 528-34.

การตอบสนองของพรอสเตรต สเปซิฟิก แอนติเจน ในผู้ป่วยมะเร็งต่อมลูกหมาก ระยะแพร่กระจายไปกระดูกหลังการรักษาโดยการตัดลูกอัณฑะออกทั้ง 2 ข้าง

สุนัย ลีวันแสงทอง, พบ, สุชาย สุนทราภา, พบ**

วัตถุประสงค์ : เพื่อศึกษารูปแบบการตอบสนองของพรอสเตรต สเปซิฟิก แอนติเจน (PSA) และปัจจัยเสี่ยงต่าง ๆ ในผู้ป่วยมะเร็งต่อมลูกหมากระยะแพร่กระจายไปกระดูกหลังการรักษาโดยการตัดลูกอัณฑะออกทั้ง 2 ข้าง

วัตถุและวิธีการ : ศึกษาในผู้ป่วยมะเร็งต่อมลูกหมากระยะแพร่กระจายไปกระดูก จำนวน 44 ราย ผู้ป่วยทุกรายได้รับการผ่าตัดลูกอัณฑะออกทั้ง 2 ข้างและได้รับการเจาะเลือดติดตามค่า PSA หลังการผ่าตัด การศึกษาสิ้นสุด ณ เวลาที่ค่า PSA สูงขึ้นในการติดตาม รูปแบบการตอบสนองของค่า PSA และปัจจัยเสี่ยงได้ถูกนำมาวิเคราะห์

ผล : ผู้ป่วยทุกรายมีค่า PSA ลดลงจนถึงระดับต่ำสุด โดยระยะเวลาโดยเฉลี่ยที่ค่า PSA ลดลงครึ่งหนึ่ง คือ 2.1 เดือน ระยะเวลาโดยเฉลี่ยที่ค่า PSA ลดลงจนถึงระดับต่ำสุด คือ 6.7 เดือน ระยะเวลาโดยเฉลี่ยที่ค่า PSA เพิ่มสูงขึ้นอีกคือ 11.2 เดือน ในขณะที่ค่า PSA เริ่มจะสูงขึ้นผู้ป่วยทุกคนยังมีชีวิตและสภาวะของมะเร็งทางคลินิกยังไม่ลุกลามมากขึ้น ปัจจัยเสี่ยงที่สำคัญ คือระดับความรุนแรงของพยาธิสภาพของมะเร็ง ระยะเวลาโดยเฉลี่ยที่ค่า PSA สูงขึ้นในผู้ป่วยที่มีระดับความรุนแรงของพยาธิสภาพของมะเร็งที่ดี คือ 19.3 เดือน ในขณะที่ระยะเวลาโดยเฉลี่ยที่ค่า PSA สูงขึ้นในผู้ป่วยที่มีระดับความรุนแรงของพยาธิสภาพของมะเร็งปานกลางและผู้ป่วยที่มีระดับความรุนแรงของพยาธิสภาพของมะเร็งรุนแรง คือ 10 เดือน และ 9.3 เดือนตามลำดับ

สรุป : ค่า PSA จะลดลงหลังการผ่าตัดลูกอัณฑะออกทั้ง 2 ข้าง ในผู้ป่วยมะเร็งต่อมลูกหมาก ระยะแพร่กระจายไปกระดูกแล้ว โดยค่า PSA จะลดลงสู่ระดับต่ำสุด ในระยะเวลาโดยเฉลี่ย 6 ถึง 7 เดือน และจะอยู่คงที่ได้ระยะหนึ่ง หลังจากนั้น ค่า PSA จะสูงขึ้นอีก ผู้ป่วยที่มีระดับความรุนแรงของพยาธิสภาพที่ดีจะได้ผลในการรักษาดีกว่าผู้ป่วยที่มีระดับความรุนแรงของพยาธิสภาพปานกลางหรือระดับความรุนแรงของพยาธิสภาพที่รุนแรง

คำสำคัญ : พรอสเตรต สเปซิฟิก แอนติเจน, ต่อมลูกหมาก, มะเร็งต่อมลูกหมาก

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