JOURNAL OF ANKARA MEDICAL SCHOOL Vol 23, No 3, 2001 221-226

THE RELATIONSHIP POSTTHERAPEUTIC SERUM PROSTATE-SPECIFIC ANTIGEN LEVELS AND OVERALL SURVICAL IN PATIENTS WITH HORMONE-REFRACTORY PROSTATE CANCER

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SUMMARY

The aim of this study was to determine the relation between survival and variations in prostate-specific antigen levels, an objective criterion for estimation of survival in patients with hormone-refractory prostate cancer. Twenty-four patients with hormone-refractory prostate cancer were administered epirubicine 30mg/m2 intravenously weekly for eight weeks and then monthly for four to six months, along with oral administration of 560mg estramustine.

The mean length of survival was 9.3 months in the nine patients (37,5%) whose prostate-specific antigen levels increased during the treatment, 13 months in the eight patients (33,5%) whose prostate-specific antigen levels decreased by 0-50% and 19 months in the seven patients (29%) whose prostate-specific antigen levels decreased by 50% or more. The mean length of survival was significantly longer in patients whose prostate-specific antigen levels decreased by more than 50% when compared to those whose prostate-specific antigen levels decreased by less than 50% or increased ($p<0.001$). It can be concluded that prostate-specific antigen levels can be considered a reliable indicator for prognosis during treatment of hormone-refractory prostate cancer.

Key words: *Hormone-Refractory Prostate Cancer, Prostate-Specific Antigen.*

ÖZET

HORMON REZİSTAN PROSTAT KANSERLİ HASTALARDA TEDAVİ SONRASI PSA DEĞİŞİMİNİN YAŞAM SÜRESİ İLE İLİŞKİSİ

Bu çalışma, hormona rezistan prostat kanserli (HRPK) hastaların yaşam sürelerinin tahmininde objektif bir kriter olan PSA değerlerinin değişimi ile yaşam süresi arasındaki ilişkiyi belirlemek amacıyla planlandı. Hormona rezistan prostat kanserli 24 hastaya sistemik epirubisin tedavisi ile birlikte oral estramustin tedavisi uygulandı. Epirubisin 30 mg /m2 dozunda haftada bir kez sekiz hafta süreyle verildi ve daha sonra 4- 6 ay kadar süre ile ayda bir kez tekrarlandı. İlave olarak 560 mg dozda ve oral yolla estramustin fosfat uygulandı.

Tedavi sırasında PSA sı yükselen 9 hastanın (% 37,5) ortalama yaşam süresi 9,3 aydı. PSA değeri % 0-50 arasında azalan 8 hastanın (%33,5) ortalama yaşam süresi 13 ay olarak tesbit edildi. Buna karşılık PSA sı % 50 den fazla azalan 7 (%29) hastada ise 19 aylık bir yaşam süresi elde edildi.

PSA sı % 50 en fazla azalan hastaların ortalama yaşam süresi daha az azalan veya artan hastalara göre anlamlı olarak yüksek bulundu ($P< 0,001$). PSA hormona refrakter prostat kanserinin tedavisi sırasında prognoz göstergesi olarak güvenilebilir bir parametre olarak kabul edilebilir.

Anahtar Kelimeler: *Hormona Dirençli Prostat Kanseri, Prostat Spesifik Antijen*

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Received: June 19,2001 Accepted: July 17,2001

It has been suggested that prostate-specific antigen (PSA), employed as an objective parameter in diagnosing and evaluating treatment of prostate cancer, can also be used in assessing the response to treatment of hormone-resistant prostate cancer (HRPC). Due to the difficulties and costs involved in assessing the response to treatment according to WHO criteria (1), various studies have attempted to determine the reliability of PSA results by themselves, both for estimating prognosis and for demonstrating the efficacy of drugs used in treatment (2,3).

The aim of the present study was to determine the changes in PSA levels after the administration of epirubicine and estramustine phosphate in HRPC cases and the effect of these changes on prognosis.

MATERIALS AND METHODS

The study comprised 24 patients diagnosed with HRPC between August 1998-January 2001. Data on the pre-chemotherapy status of the patients is outlined in (Table 1).

Patient age ranged from 49-79 years (mean: 66 years). Initially, 13 patients underwent bilateral orchiectomy and 11 patients were administered one of the LHRH analogues. All patients were exposed to maximal androgen blockage, using flutamid or biculamid. Patients with increases in PSA levels and progression in pain

Table 1: Characteristics of Patients Before Treatment

CHARACTERISTICS	
Number of Patients	24
Mean Age	66 years (49-79years)
Previous Treatment	
-Orchiectomy+M.A.B.*	13
-M.A.B. with LHRH analogues	11
Mean Time of Progression	17 months (6-40months)
Measurable Lesions	
-LAP	4
-Liver Metastasis	2
Urinary Obstruction	3
Pain Score	
0	3
1	14
2	7
Mean Pain Score	1.27
Performance Score	
0	13
1	9
2	2
Mean Performance Score	0.52
Mean PSA Value on Diagnosis of HRPC	110 (9-520) (g/ml

* M.A.B. = Maximal androgen blockage

and performance scores during regular controls requested once-a-month visits for PSA analyses and bone scintigraphy. Patients with significant increases in at least two PSA measurements and increases in lesions in bone scintigraphy after the initiation of treatment were considered to have HRPC. Patients treated with LHRH analogues underwent bilateral orchiectomy after being diagnosed with HRPC.

Disease progression ranged from 6 to 40 months (mean 17 months). Patients with a pain score greater than 3 and a performance score greater than 2 according to WHO criteria were not included in the study (1). Patients taking medication for obvious heart disease or serious disorders in renal functions were also excluded, as were six patients whose medication was administered irregularly due to estramustine-related gastrointestinal problems. At the baseline of the study, the mean pain score was found to be 1.27 and the mean performance score 0.52.

Prior to treatment, all patients underwent routine blood analysis, ultrasonography, IVP, lung radiography, PSA and alkaline phosphatase analyses, EKG and bone scintigraphy. Cardiology consultation was requested due to the possibility of cardio-respiratory dysfunction as a result of drug administration.

During treatment, 30 mg/m2 epuribicine was administered weekly for eight weeks and then monthly for four to six months. In conjunction with epirubicine, 560 mg estramustine phosphate was administered orally. Patients were informed about the possible effects of these drugs. A CBC was performed every two weeks during treatment. PSA analysis was repeated every month. Pain and performance scores and PSA results were evaluated within the first month of treatment and subsequently every three months. Estramustine was continued in patients who completed weekly and monthly epirubicine therapy until general performance decreased to a level at which patients could not tolerate oral nutrition. After this stage, therapy was limited to symptom management. The same protocol was applied to patients with increases in PSA levels.

The mean follow-up time was 15.2 months for all patients. Results were evaluated using 't' statistical analysis.

RESULTS

Three months after initiation of treatment, pain and performance scores improved at least one point in all patients. Pain scores decreased from 1.27 to 0.22 ($p<0.001$) and performance scores decreased from 0.52 to 0.08 ($p< 0.001$) (Figure 1).

However, PSA values were observed to increase in nine patients (37.5%), although their subjective complaints improved by at least one point (Table 2). The mean length of survival of these patients was 9.3 months (Figure 2).

PSA level decreased by 0-50% in eight patients (33.5%) and continued to decrease for a mean of five months (2-12 months). The mean length of survival of these patients was 13 months (Figure 2).

PSA level decreased by more than 50% in seven patients (29%). Low levels of PSA were observed to be maintained for a mean of 10 months (7-30 months). It decreased by more than 80% in four patients. Those patients who are still alive have been followed for 12, 15, 18 and 30 months, respectively, and low PSA levels are still maintained in two of these patients. The mean survival of this group is 19 months (12-30 months) (Figure 2).

There was no significant difference in the mean survival between patients whose PSA levels increased and those whose PSA levels decreased by less than 50%. However, there was a significant difference between patients whose PSA levels decreased by more than 50% and those whose PSA levels increased ($p<0.001$).

At the end of six months, pain and performance scores increased in seven patients. Of these, five had high PSA levels and two had PSA levels that had decreased by 0-50%. One patient from each group died at the end of six months. At the end of nine months, 55% of patients had increased pain and performance scores. Two patients with increased PSA levels died. At the

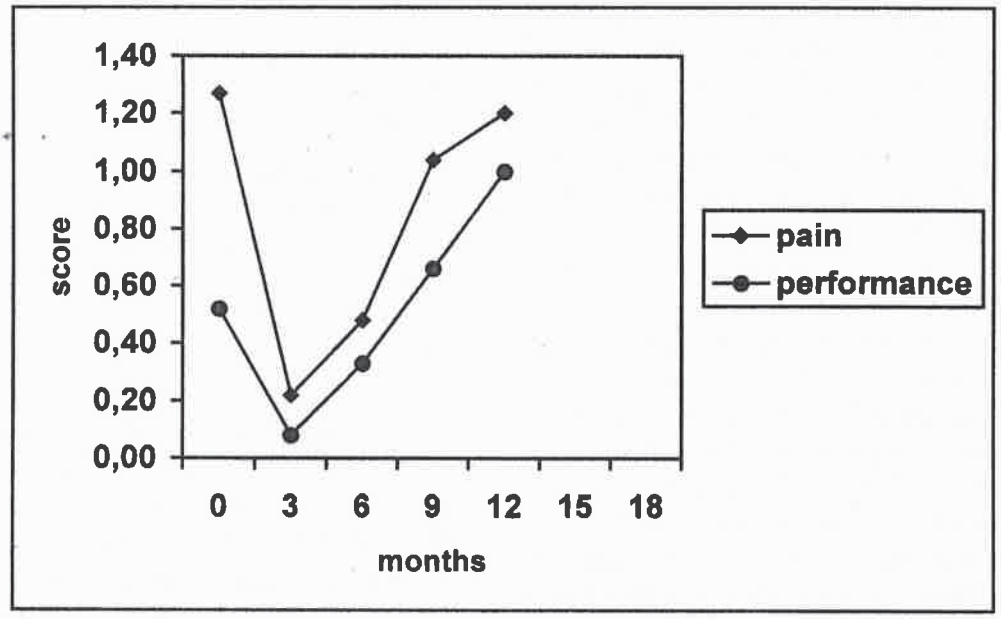

Figure 1: Distribution of Pain and Performance Scores of Patients During Treatment According to Months

end of one year, it was established that subjective complaints increased from a mean of 8.4 months on. Four patients whose PSA levels fell by more than 50% are still alive, and their mean follow-up is 19 months as of the present. PSA levels of two of these patients continue to remain within a normal range, while the other two have normal pain and performance scores but a slight increase in PSA. One of these patients with a decrease of 0-50% in PSA levels in the 15th month of follow-up was found to have normal pain and performance scores but a significant increase in PSA. The average survey of the 19 patients who died due to the disease was 12.7 months.

The decrease in PSA continued for a mean of five months in patients with 0-50% PSA suppression and 10 months in patients with greater than 50% PSA suppression. However, the number of patients was not high enough to perform a statistical analysis. The duration of PSA supression was longer in patients with more than a 50% decrease in PSA levels, particularly in those with more than an 80% decrease.

Four patients whose PSA levels increased or decreased by 0-50%. had feet oedema due to ultrasonographically detected LAP; this regressed for up to six months but recurred later. Two

Table 2: Changes in PSA During Treatment and Mean Survival

Changes in PSA	Number of Patients	Length of Time Changes Sustained	Mean Survival
Increase in PSA	9 (37.5%)	-	9.3 (6-24) months
Decrease in PSA by 0-50%	8 (33.5%)	5 months (mean)	13 (6-24) months
Decrease in PSA by more than 50%	7 (29%)	10 months (mean)	19 (12-30) months

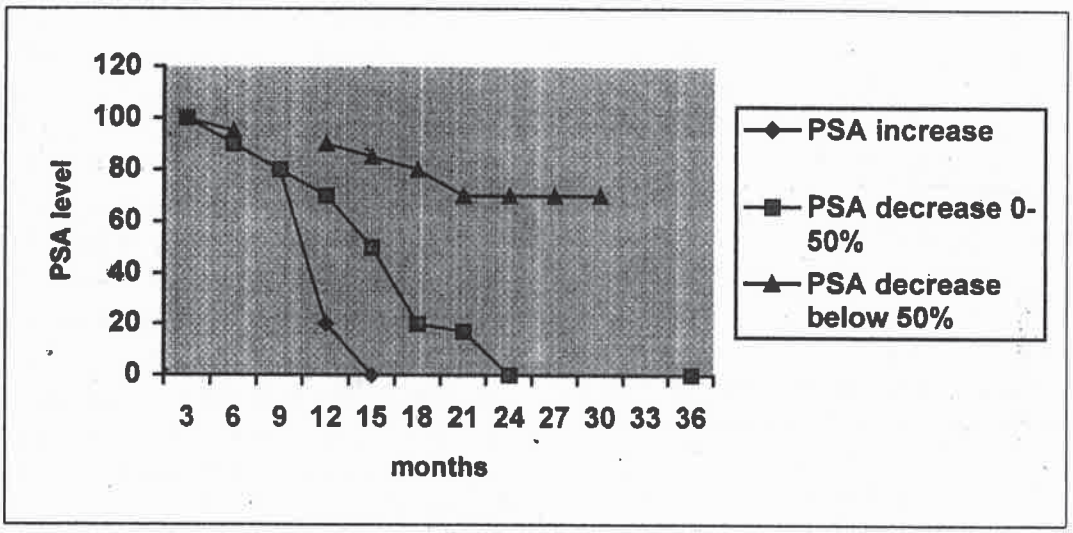

Figure 2: PSA Changes and Survival of Patients

patients whose PSA levels decreased by 0-50% had liver metastasis that did not regress during therapy and died after 12 and 16 months, respectively. Three patients underwent percutaneus nephrostomy due to urinary obstruction. The nephrostomy catheter was removed after 45 days from one of these patients, whose PSA level decreased by more than 50% due to regression of obstruction in antegrad pyelography. The PSA levels of the other two patients increased despite the therapy, with no change in obstruction.

During therapy, two patients experienced cardiotoxic side effects and died as a result of heart failure. Gastrointestinal side effects due to estramustine were observed in eight patients, whose therapy was discontinued for short intervals. Four patients received blood transfusions for anemia. We observed changes in pigmentation in one patient and painless gynecomastie in five patients caused by epirubicine.

DISCUSSION

Since the recognition of the significance of PSA in prostate cancer, PSA has been used in the evaluation of cytotoxic treatment administered in HRPC (4). Nevertheless, the interpretation of changes in PSA levels has not been standardized to date.

Culine et al. observed a decrease in PSA levels of 50% of their 31 patients treated with estramustine and 20 mg/m2 doxorubicine weekly. The decrease continued for three months, and the mean length of survival was 12 months (2). Hermes et al. maintained a decrease in PSA levels of 50% in 54% of their 24 HRPC patients treated with 100 mg epirubicin/m2 and estramustine. The decrease continued for three months, and the mean length of survival was 13.2 months (3). In their 110 HRPC cases, Kelly et al determined that those patients with a minimum 50% decrease in PSA levels at 60 days after initiation of treatment had longer survival rates (5). In his study using estramustine phosphate and vinblastine, Hudes obtained similar results (6). In a Phase II study evaluating 114 patients treated with estramustine phosphate and etoposide, a decrease of more than 50% in PSA levels in the eighth month of treatment when compared to baseline values was associated with an increase in survival length (7). The mean length of survival of patients whose PSA levels decreased by more than 50% was 91 weeks, compared to 38 weeks in the remaining patients in the study. Schultz et al suggest that a decrease of 80% in PSA levels is more valuable than a 50% decrease in determining survival lengths (8).

In the present study, a significant difference was found between patients whose PSA levels increased and those whose PSA levels decreased more than 50%. Moreover, four patients whose PSA levels decreased more than 80% could be followed with normal PSA levels. Thus, consistent with the literature, we can also assert that a decrease of more than 80% in PSA levels is related to higher survival.

The mechanism by which PSA levels decrease is not clearly understood (9). However, PSA is known to be released under the control of hormones. Androgen receptors regulate the expression of PSA by linking with androgen-response components. Other factors that regulate PSA expression include Vitamin D, Transforming Growth Factor, Basic Fibroblast Growth Factor and Proteinchinase C. Any component that influences these agents can affect PSA level, irrespective of cell death. Thus, in order to evaluate the results, changes in PSA level must be investigated in terms of three criteria: the rate of decrease in PSA levels; the time to decrease in PSA levels; and the length of time over which the decrease is maintained. As stated, previously published articles have asserted that a reduction of over 80% in PSA levels has positive impact on survival. Another study showed that a decrease in PSA levels of more than 50% that is maintained for over one year is more significant in terms of survival than a decrease of 80% maintained for two months (9).

In conclusion, PSA may be used as an important objective parameter in evaluating treatment of HRPC.

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