PSA Kinetics Provide Improved Prediction of Survival in Metastatic Hormone-Refractory Prostate Cancer

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OBJECTIVES To assess the value of prostate-specific antigen (PSA) kinetics in predicting survival and relate this to the baseline variables in men with metastatic hormone-refractory prostate cancer (HRPC).

METHODS The data from 417 men with HRPC were included in a logistic regression model that included hemoglobin, PSA, alkaline phosphatase, Soloway score, and performance status pain analgesic score at baseline. The posttreatment variables included the PSA level halving time after the start of treatment, PSA level at nadir, interval to nadir, PSA velocity (PSAV), PSA doubling time after reaching a nadir, patient age, and treatment. These variables were added to the baseline model, forming new logistic regression models that were tested for net reclassification improvement.

RESULTS The area under the receiver operating characteristics curve for the baseline model was 0.67. Of all variables related to PSA kinetics, the PSAV was the best predictor. The addition of PSAV to the baseline model increased the area under the receiver operating characteristics curve to 0.81. Only a moderate increase in the area under the receiver operating characteristics curve (0.83) was achieved by combining the baseline model in a multivariate model with PSAV, PSA doubling time, interval to nadir, and patient age at diagnosis of HRPC.

CONCLUSIONS The PSAV alone gave a better prediction of survival value than all other PSA kinetics variables. By combining PSAV with the variables available at baseline, a better ground for treatment decision-making in men with HRPC can be achieved. UROLOGY 72: 903–907, 2008. © 2008 Elsevier Inc.

Prostate cancer is currently the most frequent malignancy in men and is responsible for the second greatest number of cancer-related deaths after lung cancer.[1] The American Cancer Society has estimated that 218 890 new cases were diagnosed in the United States during 2007 and that more 27 000 men will die of prostate cancer.[1]

The response rate to androgen deprivation therapy for men with metastatic disease is 80%-90%. Eventually, almost all these men develop hormone-refractory prostate cancer (HRPC). The median survival from the diagnosis of metastatic disease until death is about 2.5-3.2 years.[2-4]

Until recently, prostate cancer was considered to be a chemoresistant disease. However, randomized trials have shown that docetaxel-based regimens offer a survival benefit.[5,6] Because the prolongation of survival is modest and significant toxicity is associated with the treatment, a more reliable predictor of survival would be of great value to enable better risk group stratification. Group identification could make it possible to predict which patients can expect the greatest benefit from treatment. A low hemoglobin, high alkaline phosphatase (ALP), and poor performance status at diagnosis have been associated with short survival of patients with metastatic HRPC.[7-9]

The addition of PSA kinetics to these baseline variables has been studied. A short PSA doubling time (PSA-DT) has been shown to be associated with short survival.[10-12] A high PSA velocity (PSAV) is associated with short survival in men with metastatic HRPC.[10,13] A

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long PSA response duration and a low PSA nadir has been associated with increased survival.[8,14]

In a previous study, we described how early serial measurement of PSA and ALP during primary androgen deprivation therapy could predict for survival in metastatic prostate cancer.[15] The aim of this study was to determine whether PSA kinetics provide a reliable prediction of survival in men with HRPC and to compare the PSA kinetics with the baseline variables routinely used for decision-making.

MATERIAL AND METHODS

The present study included 915 patients with metastatic prostate carcinoma (M1) and World Health Organization performance status of 0-2, who were recruited, from December 1992 to June 1997, to a study designed to compare parenteral estrogen with total androgen blockade undertaken by the Scandinavian Prostate Cancer Group, the SPCG-5 study.[16] Polyestradiol phosphate was given as intramuscular injection 240 mg twice monthly for 2 months and once a month thereafter. Total androgen blockade was given as oral flutamide, 250 mg three times daily combined with either the gonadotropin-releasing hormone analog, triptorelin, 3.75 mg/mo intramuscularly or bilateral orchiectomy. According to the original study protocol, no second-line treatment was to be started before clinical progression was firmly registered. Long-term survival of the patients in this trial has been previously reported; no significant difference in survival between the 2 groups was seen.[16] All patients were without previous systemic treatment of prostate cancer. Our definition of HRPC was 2 consecutive increases in the PSA level after the nadir.

Of the original 915 patients, 383 were excluded because of incomplete PSA follow-up. In 21 men, the cancer was primarily hormone insensitive and 10 had missing values at baseline. For 81 men, the PSA level at 6 months after nadir was lower than that at 3 months after nadir, and in 3 men, no date of nadir had been recorded. The remaining 417 constituted our study population.

PSA, ALP, and hemoglobin were determined by routine laboratory methods before the start of treatment. The PSA level was measured every third month thereafter. The normal PSA range was 0-3 ng/mL, the normal ALP level was <4.6 μkat/L and for hemoglobin 134-170 g/L. The tumor burden seen on bone scan was classified according to a modified Soloway score.[16] The performance status pain analgesic score was obtained by adding 0-5 points, pain 0-4 points, and use of analgesic 0-5 points to the World Health Organization performance status. This was used as a measure of how patients were clinically affected by the disease. The data are listed in Table 1.

These 5 variables (PSA, ALP, hemoglobin, Soloway, and performance status pain analgesic score) constituted the baseline model and benchmark against which the variables related to the PSA kinetics were compared. To determine which variable added the most prognostic information compared with the baseline model, we included the PSA nadir, PSAV, interval to nadir, PSA-DT, PSA halving time, treatment, and patient age at which HRPC was confirmed.

The median age at the start of treatment was 72.8 years. The median survival from the start of treatment was 2.66 years.

Table 1. Baseline data of 417 men with HRPC and complete follow-up stratified by survival duration

Variable	All	Dead Within 9 mo	Alive at 9 mo
Patients (n)	417	135 (32)	282 (68)
Treatment			
Polyestradiol phosphate	191 (46)	56 (42)	135 (48)
Total androgen blockade	226 (54)	79 (58)	147 (52)
Follow-up (mo)			
Mean	20.2	4.75	27.6
Median	14.7	4.73	20.8
Age at randomization (y)			
<65	70 (17)	22 (16)	48 (17)
65-69	82 (20)	30 (22)	52 (18)
70-74	115 (28)	32 (24)	83 (29)
75-79	103 (25)	36 (27)	67 (24)
≥80	47 (11)	15 (11)	32 (11)
PSA (ng/mL)			
<50	43 (10)	14 (10)	29 (10)
50-100	58 (14)	18 (13)	40 (14)
100-200	77 (18)	27 (20)	50 (18)
200-800	144 (34)	49 (36)	95 (34)
800-1500	45 (11)	12 (9)	33 (12)
>1500	50 (12)	15 (11)	35 (12)
ALP (μkat/L)			
<3	48 (12)	8 (6)	40 (14)
3-5	126 (30)	32 (24)	94 (33)
5-10	103 (25)	36 (27)	67 (24)
10-20	81 (19)	32 (24)	49 (17)
>20	59 (14)	27 (20)	32 (11)
Soloway score			
1	137 (33)	29 (22)	108 (38)
2	233 (56)	87 (64)	146 (52)
3	47 (11)	19 (14)	28 (10)
PSPA score			
0	120 (29)	30 (22)	90 (32)
1	50 (12)	9 (7)	41 (14)
2-5	168 (40)	60 (44)	108 (38)
>5	79 (19)	36 (27)	43 (15)
Hemoglobin (g/L)			
<115	59 (14)	31 (23)	28 (10)
115-130	92 (22)	33 (24)	59 (21)
130-145	158 (38)	57 (42)	101 (36)
>145	108 (26)	14 (10)	94 (33)

HRPC = hormone refractory prostate cancer; PSA = prostate-specific antigen; ALP = alkaline phosphatase; PSPA = performance status pain analgesic.

Data presented as number of patients, with percentages in parentheses, unless otherwise noted.

Ethics

The study was performed in accordance with the recommendations of the Helsinki Declaration. The ethics committee at all contributing centers approved the study. Patients were given verbal and written information, and gave their informed consent to participate in the study.

Statistical Analysis

The definitions of the posttreatment covariates were as follows:

Interval to nadir: interval from the start of treatment until the lowest PSA value was recorded. If several values were identical, the interval to when the last one was recorded was used.

PSA halving time: calculated from the PSA values taken from the start until the nadir was reached. If the lowest value was repeated, the first one was used. Using logarithmic transformation of PSA values, a slope was calculated by linear regression analysis. The halving time was calculated by dividing the slope by $-\log(2)$.

PSA-DT: calculated from the PSA values from nadir until HRPC was diagnosed. Using logarithmic transformation of PSA values, a slope was calculated by linear regression analysis. The doubling time was determined by dividing the slope with log(2).

PSA nadir: the lowest PSA value measured.

PSAV: the absolute increase in PSA (ng/mL/y) from nadir until HRPC was diagnosed.

Treatment: parenteral estrogen treatment or total androgen blockade.

Our definition of HRPC was 2 consecutive increasing PSA levels after nadir. Because the PSA level was taken every third month, it took 6 months after nadir before HRPC could be diagnosed. The PSAV and PSA-DT were calculated from the PSA values between the nadir and 6 months thereafter.

The data were dichotomized into 2 groups: dead or alive 9 months after the diagnosis of hormone-refractory disease. To begin, a baseline covariate risk model was established by a backward elimination in a logistic regression analysis using performance status pain analgesic score, hemoglobin, Soloway score, ALP, and PSA as covariates. In the analysis of the odds ratios, logarithmic transformation was performed to achieve symmetric distribution for the skewed variables, PSA, PSAV, and PSA nadir. The odds ratios were calculated by standardizing for the standard deviation of the distribution of each covariate. To evaluate the predictive ability of the various covariates and models, we studied the odds ratios, net reclassification improvement (NRI) proposed by Pencina et al.,[17] and area under the receiver operating characteristic curve.

The predicted 9-month death probability gained from the baseline model gave 3 risk groups: low risk, with a predicted probability of <0.23, corresponding to the 30% percentile of predicted risk; intermediate risk, with a predicted probability of 0.23-0.40, where 0.40 corresponds to the 70% percentile of predicted risk; and high risk, with a predicted probability >0.40.

For each of the new prognostic markers, a logistic regression model that included the baseline covariates and the new prognostic marker were fitted, and the predicted 9-month survival was calculated. The cutoff probabilities of 0.23 and 0.40 split the data into new risk categories and the NRI was calculated. The prognostic ability of each prognostic marker was tested by z-statistics. The area under the receiver operating characteristics curve (AUC) was calculated using the c-statistic,[18] a nonparametric estimate of the area under the receiver operating characteristics curve.

RESULTS

The interval to nadir, PSA-DT, and PSAV were the variables with the greatest odds ratios to predict death within 9 months. The log (PSA) at baseline, PSA halving time, patient age at HRPC diagnosis, and treatment had no predictive power (Table 2). ALP was excluded from the baseline model, because it had no predictive power in the multivariate logistic regression model (data not shown). The PSAV gave the greatest NRI when added to the baseline model (NRI = 0.35, AUC = 0.81), followed by the interval to nadir (NRI = 0.27, AUC = 0.76) and PSA-DT (NRI = 0.25, AUC = 0.76). When all the baseline variables were included in a multivariate model, together with the PSAV, interval to nadir, PSA-DT, and age at which HRPC was diagnosed, the NRI was 0.39, with an AUC of 0.83 (Table 3). The NRI calculation for the baseline model plus PSAV is shown in Table 4. The first (Q1), median (Q2), and third (Q3) quartile for the PSAV was 0.52 ng/mL, 2.6 ng/mL, and 12.6 ng/mL/mo. The median survival was 26.4 months for men with a PSAV less than Q1, 17.1 months for men with a PSAV between Q1 and Q2, 12.3 months for men with a PSAV between Q2 and Q3, and 6.2 months for men with a PSAV greater than Q3.

Table 2. Univariate logistic regression analysis of studied variables to predict risk of death within 9 months of HRPC diagnosis

Model Characteristic	OR (95% CI)	*P* Value
Log(PSA) level at baseline, per SD decrease	1.09 (0.89-1.34)	0.39
Soloway score (1 = reference)		
2	2.22 (1.36-3.62)	.001
3	2.53 (1.24-5.15)	.011
Hemoglobin at baseline per SD decrease	1.60 (1.29-2.00)	<.001
ALP at baseline per SD increase	1.39 (1.13-1.70)	.002
PSPA per SD increase	1.45 (1.18-1.78)	<.001
HRPC age per SD decrease	1.01 (0.82-1.24)	.91
Treatment	1.30 (0.86-1.96)	.22
Interval to nadir per SD decrease	3.51 (2.35-5.24)	<.001
PSA halving time per SD increase	1.03 (0.85-1.26)	.76
PSA-DT per SD decrease	4.69 (2.59-8.47)	<.001
Log(PSA nadir) per SD increase	1.51 (1.22-1.86)	<.001
Log(PSAV) per SD increase	3.05 (2.33-3.99)	<.001

OR = odds ratio; CI = confidence interval; SD = standard deviation; PSA-DT = PSA doubling time; PSAV = PSA velocity; other abbreviations as in Table 1.

COMMENT

When introducing a new prognostic marker, the predictive ability of the markers that are already established in clinical practice should be considered as benchmarks for comparison. By quantifying any improvement using NRI, the clinical value of the new marker can be determined. Our results showed the baseline model to provide prognostic information with an AUC of 0.67; however, when the PSAV was added to the model, the NRI was 0.35 and the AUC became 0.81. This implies that PSAV gives a reliable prediction of survival in men with HRPC. When all combinations of the PSA kinetic variables were tested, the maximal NRI was 0.39 and the corresponding AUC was 0.83 in the multivariate model. Because the

Table 3. Net reclassification improvement for PSA kinetics variables, HRPC age, and treatment when added to baseline variables

Variable	NRI	z-Statistic	*P* Value	AUC
Baseline variables plus	—	—	—	0.67
PSA nadir	0.09	1.51	.13	0.70
PSAV	0.35	4.89	<.001	0.81
Interval to nadir	0.27	3.93	<.001	0.76
Treatment	0.01	0.38	.70	0.68
PSA halving time	0.00	−0.27	.78	0.67
PSA-DT	0.25	3.73	<.001	0.76
HRPC age	0.00	−0.22	.83	0.67
Multivariate model with baseline variables and PSAV, PSA-DT, interval to nadir and HRPC age	0.39	5.05	<.001	0.83
Baseline variables plus	—	—	—	—
PSA nadir + PSAV	0.34	4.67	<.001	0.81
PSA nadir + interval to nadir	0.25	3.60	<.001	0.76
PSA nadir + PSA-DT	0.30	4.43	<.001	0.79
PSAV + interval to nadir	0.35	4.76	<.001	0.82
PSAV + PSA-DT	0.32	4.44	<.001	0.81
Interval to nadir + PSA-DT	0.35	4.84	<.001	0.80

NRI = net reclassification improvement; other abbreviations as in Tables 1 and 2.

Prognostic ability for each prognostic marker shown by z-statistics, with corresponding *P* value and area under receiver operating characteristics curve.

Table 4. Baseline model and baseline model, including PSAV, in NRI model

	Baseline Model Plus PSAV			
Baseline Model (Risk Group)	Risk Group 1	Risk Group 2	Risk Group 3	Total
Alive at 9 mo				
1	80	18	6	104
2	64	28	27	119
3	19	19	21	59
Total	163	65	54	282
Dead within 9 mo				
1	10	3	5	18
2	10	20	33	63
3	3	5	46	54
Total	23	28	84	135

PSAV = prostate-specific antigen velocity; NRI net reclassification improvement; risk group 1 = low risk; risk group 2 = intermediate risk; risk group 3 = high risk.

For men with no event, a change from a lower to a higher risk group (18 + 6 + 27) when adding PSAV should be interpreted as an unfavorable reclassification and a change from a higher to a lower risk group (64 + 19 + 19) as a favorable reclassification.

For men with a recorded event, the interpretation is the opposite: a change from a lower to higher risk group (3 + 5 + 33) implies a favorable reclassification and a change from a higher to a lower risk group (10 + 3 + 5) indicates an unfavorable reclassification.

The NRI is calculated as follows: NRI = [(3 + 5 + 33)/135 − (10 + 3 + 5)/135] − [(18 + 6 + 27)/282 − (64 + 19 + 19)/282] = (41/135 − 18/135) − (51/282 − 102/282) = 0.351.

PSAV alone gave almost the same increase as all other variables put together, this variable can be considered a major predictor of the disease course in clinical practice, as well as in research. Several nomograms have been developed to predict prostate cancer-related outcomes and have proved to be of great use in treatment decision-making.[19] Two nomograms are available for the prediction of survival in men with metastatic HRPC, both using pretreatment variables only.[7,9] Smaletz et al.[9] found an AUC of 0.71, and an AUC of 0.69 was seen in the study by Halabi et al.[7] Our baseline model AUC was basically the same, but the addition of PSA kinetic variables caused the AUC to increase considerably.

In the retrospective study on a case mix of M1, M0, and Mx tumors using multivariate Cox proportional hazard analysis by Daskivich et al.,[10] it was shown that the PSA-DT and PSAV provided additional information regarding prognosis in men with HRPC. Oudard et al.[11] found that a short PSA-DT was associated with short survival in a retrospective study of men treated with chemotherapy for metastatic HRPC. The PSAV was not included in that study. A similar study by Semeniuk et al.,[12] with the difference that some of their patients had undergone radiotherapy, gave results that were basically the same. Rozhansky et al.,[13] using multivariate Cox analysis, showed that the PSAV was associated with survival in men with HRPC treated with cytotoxic, cytostatic, or combination therapy.

A limiting factor in our study was that the PSA values were taken every third month, but this seemed reasonable as long as the PSA level was low and did not rise. When the nadir was reached, the next PSA measurement was taken 3 months later. In retrospect, one could argue that the subsequent PSA levels should have been measured more frequently to reveal 2 values increasing as quickly as possible after the nadir. This, however, would not have affected the ability of NRI to evaluate new variables and their power to predict the outcome accurately.

The ability to provide prognostic information in men with HRPC is essential for randomized clinical trials in which homogenous groups with similar survival data before the onset of the trial are required. Furthermore, if physicians are to recommend treatment to their patients they must have some idea of the individual patient's

prognosis. PSAV should be included as a prognostic marker in future studies of men with metastatic HRPC.

CONCLUSIONS

Of all the variables we studied, the PSAV was the single most reliable predictor of survival in PSA kinetic men with metastatic HRPC. This was confirmed by applying the NRI, which makes it possible to evaluate how much new predictive information a variable adds to a model. Together with the other variables available before the start of treatment, the PSAV might be helpful in clinical decision-making, as well as stratification in clinical studies. However, additional validation studies are needed to confirm these findings.

References

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2007. *CA Cancer J Clin.* 2007;57:43-66.
2. Aus G, Robinson D, Rosell J, et al. Survival in prostate carcinoma—Outcomes from a prospective, population-based cohort of 8887 men with up to 15 years of follow-up: Results from three countries in the population-based National Prostate Cancer Registry of Sweden. *Cancer.* 2005;103:943-951.
3. Collette L, de Reijke TM, Schroder FH. Prostate specific antigen: A prognostic marker of survival in good prognosis metastatic prostate cancer? (EORTC 30892). *Eur Urol.* 2003;44:182-189.
4. Glass TR, Tangen CM, Crawford ED, et al. Metastatic carcinoma of the prostate: Identifying prognostic groups using recursive partitioning. *J Urol.* 2003;169:164-169.
5. Fossa SD, Jacobsen AB, Ginman C, et al. Weekly docetaxel and prednisolone versus prednisolone alone in androgen-independent prostate cancer: A randomized phase II study. *Eur Urol.* 2007;52:1691-1698.
6. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med.* 2004;351:1502-1512.
7. Halabi S, Small EJ, Kantoff PW, et al. Prognostic model for predicting survival in men with hormone-refractory metastatic prostate cancer. *J Clin Oncol.* 2003;21:1232-1237.
8. D'Amico AV, Chen MH, Cox MC, et al. Prostate-specific antigen response duration and risk of death for patients with hormone-refractory metastatic prostate cancer. *Urology.* 2005;66:571-576.
9. Smaletz O, Scher HI, Small EJ, et al. Nomogram for overall survival of patients with progressive metastatic prostate cancer after castration. *J Clin Oncol.* 2002;20:3972-3982.
10. Daskivich TJ, Regan MM, Oh WK. Distinct prognostic role of prostate-specific antigen doubling time and velocity at emergence of androgen independence in patients treated with chemotherapy. *Urology.* 2007;70:527-531.
11. Oudard S, Banu E, Scotte F, et al. Prostate-specific antigen doubling time before onset of chemotherapy as a predictor of survival for hormone-refractory prostate cancer patients. *Ann Oncol.* 2007;18:1828-1833.
12. Semeniuk RC, Venner PM, North S. Prostate-specific antigen doubling time is associated with survival in men with hormone-refractory prostate cancer. *Urology.* 2006;68:565-569.
13. Rozhansky F, Chen MH, Cox MC, et al. Prostate-specific antigen velocity and survival for patients with hormone-refractory metastatic prostate carcinoma. *Cancer.* 2006;106:63-67.
14. Hussain M, Tangen CM, Higano C, et al. Absolute prostate-specific antigen value after androgen deprivation is a strong independent predictor of survival in new metastatic prostate cancer: Data from Southwest Oncology Group trial 9346 (INT-0162). *J Clin Oncol.* 2006;24:3984-3990.
15. Robinson D, Sandblom G, Johansson R, et al. Prediction of survival of metastatic prostate cancer based on early serial measurements of prostate specific antigen and alkaline phosphatase. *J Urol.* 2008;179:117-123.
16. Hedlund PO, Henriksson P. Parenteral estrogen versus total androgen ablation in the treatment of advanced prostate carcinoma: Effects on overall survival and cardiovascular mortality. The Scandinavian Prostatic Cancer Group (SPCG)-5 trial study. *Urology.* 2000;55:328-333.
17. Pencina MJ, D'Agostino RBS, D'Agostino RBJ, et al. Evaluating the added predictive ability of a new marker: From area under the ROC curve to reclassification and beyond. *Stat Med.* 2008;27:157-172.
18. Hosmer DW, Lemeshow S. *Applied Logistic Regression*, 2nd ed. New York: John Wiley & Sons; 2000:160-164.
19. Chun FK, Karakiewicz PI, Huland H, et al. Role of nomograms for prostate cancer in 2007. *World J Urol.* 2007;25:131-142.