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Prediction of Response to Androgen Deprivation Therapy and Castration Resistance in Primary Metastatic Prostate Cancer

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Key Words

Prostate cancer · Bone metastasis · Androgen deprivation therapy · Duration of response · Nadir PSA · Time to nadir PSA · Castration resistance

Abstract

Purpose: We tried to establish the predictive factors influencing the initial response, as well as its duration, and time to castration resistance (CR) for primary advanced prostate cancer (PC) with bone metastasis. ***Methods:*** We evaluated all patients initially receiving androgen deprivation therapy (ADT) for primary advanced PC with bone metastasis. A total of 982 patients with complete medical records available for analysis from 18 centers were included in this study. Age, initial PSA, Gleason score (GS) and extent of bone involvement (EBI) were recorded in a database. ***Results:*** Among all the patients, 896 (91.2%) responded to ADT initially. Pretreatment PSA and EBI were significant predictors in the multivariate model. Among the 659 patients who progressed into a CR state, the mean duration of response was 22.4 months. There was a significant correlation between the CR state and nadir PSA (nPSA) level and time to nPSA. Pretreatment PSA, EBI, GS, highest tumor volume in biopsy cores (%), number of positive biopsy cores, percent positive biopsy cores and time to nPSA were proven to be significant to predict a nPSA. Pretreatment PSA, GS and EBI were statistically significant predictors of PSA normalization in multivariate analysis. The limitation of the study depends on the retrospective design and a model was developed for low standardization as a result of using multicenter data. The patients enrolled in this study were from a relatively long period of time (1989–2008). ***Conclusions:*** The results of this study indicate that it is possible to predict the initial response to ADT by pretreatment

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PSA levels and EBI, while the duration of response can be reflected by a multitude of clinical factors including nPSA, TTnPSA, percent positive cores, biopsy GS and EBI.

Introduction

Androgen deprivation therapy (ADT) is the standard and most effective palliative treatment for primary advanced prostate cancer (PC) with bone metastasis. Although PC is accepted to be an androgen-dependent tumor, initial ADT is effective in approximately 70–90% of patients with metastatic disease and the great majority of these patients will relapse subsequently with the emergence of castration resistance (CR) [1–7].

In one of the largest and relatively homogeneous (primary advanced disease with bone metastasis) retrospective multicenter study, we tried to establish the predictive factors influencing the initial response as well as its duration (the median time to biochemical progression) and time to CR.

Patients and Methods

Patient Selection and Data Collection

We evaluated all patients initially receiving ADT for primary advanced PC with bone metastasis. A total of 982 patients with complete medical records available for analysis from 18 centers were included in this study. Age, initial PSA, Gleason score (GS) and extent of bone involvement (EBI) were recorded in a database as well as the number of positive core(s), positive/total core ratio (%) and highest tumor volume in biopsy cores (%). Bone metastasis was diagnosed by bone scans routinely and additional MRI was performed if indicated.

Inclusion Criteria

Patients with histologically proven adenocarcinoma of the prostate and positive scans for the presence of bone metastasis who did not receive any previous treatment were included in this study.

Exclusion Criteria

Patients with solid organ metastasis (lung and/or liver) and inadequate data which were required for this study to predict the end-points were excluded.

Definitions

The following definitions were used for the end-points in this study. *Initial response:* decrease in PSA by ≥50% from pretreatment value lasting ≥1 month. *PSA 'normalization':* reaching a PSA level of ≤4 ng/ml during the treatment. *Nadir PSA (nPSA):* the lowest value of serum PSA observed during the treatment. *Time to nPSA (TTnPSA):* duration between the dates of initiation of ADT and nPSA. *Progression to CR:* two consecutive increases in PSA by ≥25% of the nadir value if nPSA ≥4 ng/ml or increase in PSA >4 ng/ml. The date of CR was chosen to be the date of the first PSA increase. *Duration of response (time to CR):* the period from the initiation of ADT to CR.

Follow-Up

Response to treatment in each patient was monitored every 3 months by determination of serum PSA levels.

End-Points

Primary end-points were used to establish the predictors of initial response to ADT, duration of response and CR. Secondary end-points were to detect the factors influencing nPSA or reaching PSA <4 ng/ml after ADT.

Statistical Methods

The patient characteristics were summarized as the number of patients with the percentage or as the mean with standard deviation. Student's t test and χ^2 test were used to evaluate the significance between groups due to initial response using the variables. Univariate logistic regression analyses were used for each covariate predicting end-point. Multivariate analyses were constructed using the significant covariates from the univariate analyses. Statistical significance was considered at $p < 0.05$ by using SPSS software (SPSS Inc., Chicago, Ill., USA).

Results

Patient Characteristics

Between April 1989 and April 2008, 982 patients with primary metastatic PC from 18 centers were enrolled in this study. The median age of all patients at initiation of ADT was 68 years (range 45–88). Patients were stratified according to initial response to ADT into two groups. Pretreatment patient disease characteristics are summarized in table 1.

Initial Response to ADT

Among all patients, 896 (91.2%) responded to ADT initially. When responders and non-responders were compared, age, initial PSA, GS and EBI were significant for predicting the initial response to ADT in univariate logistic regression analyses. Only pretreatment PSA (≤100 vs. >100), and EBI (≤10 vs. >10) were significant predictors in the multivariate model (tables 1, 2).

The responders were also classified according to the lowest PSA levels achieved by treatment. PSA >10 ng/ml was seen in 123 (12.5%) patients, 119 (12.1%) had a value between >4 and ≤10 ng/ml, 654 (66.6%) reached PSA levels ≤4.0 ng/ml; 199 (20.3%) had a value between >1 and ≤4 ng/ml, 456 (46.3%) had PSA ≤1 ng/ml, and 260 (26.5%) achieved an undetectable PSA (<0.2 ng/ml) during ADT.

Table 1. Patient and disease characteristics according to initial response to ADT

	Response to ADT (%)	No response to ADT (%)	Total (%)	p value
Number	896 (91.2)	86 (8.8)	982	
Age	68.13 ± 8.15	65.30 ± 9.40	67.91 ± 8.28	0.003*
Pretreatment PSA, ng/ml	202.74 ± 573.98	236.87 ± 232.56	205.35 ± 555.34	0.598*
<20	174 (19.4)	9 (10.5)	183 (18.6)	0.001**
20–100	364 (40.6)	17 (19.8)	381 (38.8)	
>100	358 (40.0)	60 (69.7)	418 (42.6)	
Extent of bone involvement	7.45 ± 4.40	9.69 ± 3.28	7.63 ± 4.36	0.001*
≤10	330 (41.4)	11 (13.9)	341 (38.9)	0.001**
>10	467 (58.6)	68 (86.1)	535 (61.1)	
Gleason score	7.61 ± 1.40	7.92 ± 0.92	7.63 ± 1.37	0.061*
<7	151 (17.8)	4 (5.1)	155 (16.7)	0.011**
7	268 (31.5)	24 (30.3)	292 (31.4)	
>7	431 (50.7)	51 (64.6)	482 (51.9)	
Number of positive cores	6.22 ± 2.92	6.29 ± 2.22	6.23 ± 2.89	0.888*
Positive/total cores, %	78.22 ± 26.06	78.59 ± 21.80	78.25 ± 25.83	0.936*
Highest tumor volume in biopsy cores, %	79.18 ± 21.84	88.18 ± 11.60	80.00 ± 21.26	0.058*
ADT				0.367**
CAB	494 (55.1)	45 (52.5)	629 (64.1)	
Monotherapy	402 (44.9)	41 (47.5)	353 (35.9)	

* Student's t test. ** χ^2 test.

Table 2. Univariate and multivariate analysis for predictors of initial response to ADT

	Univariate		Multivariate	
	p	Exp(B)	p	Exp(B)
Age	0.004	0.961	0.187	0.980
Pretreatment PSA, ng/ml	0.599	1.000	–	–
Pretreatment PSA (≤100 vs. >100)	0.001	3.835	0.002	2.569
Extent of bone involvement	0.001	1.165	–	–
EBI (≤10 vs. >10)	0.001	4.355	0.002	3.071
Gleason score	0.061	1.183	–	–
Gleason score (≤7 vs. >7)	0.020	1.797	0.137	1.493
Number of positive cores	0.888	1.009	–	–
Positive/total cores, %	0.936	1.001	–	–
Highest tumor volume in biopsy cores, %	0.063	1.028	–	–
ADT (CAB vs. monotherapy)	0.650	0.900	–	–

Predictors of CR, Duration of Response

A total of 237 patients did not progress in to the CR state during a mean follow-up period of 29.9 months (median 22) in this study. Descriptive statistics of the subgroups are summarized in table 3. TTnPSA (≤6 vs. >6 months), nPSA level (≤1.0 vs. >1.0 ng/ml), percent positive cores, GS (≤7 vs. >7), and EBI (≤10 vs. >10) were all statistically significant predictors for CR in multivariate analysis (table 4).

Among the 659 patients who progressed in to a CR state, the mean duration of response was 22.4 months (median 15). There was a significant correlation between the CR state and nPSA level and TTnPSA. In patients with nPSA ≤0.2, ≤1.0, ≤4.0 and ≤10.0 ng/ml the mean

Table 3. Descriptive statistics of the subgroups according to progression to CR or not

	Response to ADT without CR (%)	CR after response (%)	p value
Number	237 (24.1)	659 (67.1)	
Age	69.81 ± 7.76	67.56 ± 8.20	0.001
Pretreatment variables			
Pretreatment PSA, ng/ml	75.95 ± 134.47	247.90 ± 658.02	0.001
<20	87 (36.5)	87 (13.2)	
20–100	94 (39.7)	270 (41.0)	0.001
>100	56 (23.8)	302 (45.8)	
Extent of bone involvement	5.88 ± 4.60	7.92 ± 4.23	0.001
≤10	108 (57.7)	222 (36.4)	0.001
>10	79 (42.3)	388 (63.6)	
Gleason score	7.34 ± 1.47	7.70 ± 1.36	0.001
<7	57 (26.3)	94 (14.8)	
7	71 (32.5)	197 (31.2)	0.001
>7	90 (41.2)	341 (53.9)	
Number of positive cores	5.45 ± 2.98	6.54 ± 2.85	0.001
Positive/total cores, %	66.49 ± 28.75	83.07 ± 23.22	0.001
Highest tumor volume in biopsy cores, %	71.41 ± 29.23	83.12 ± 15.60	0.001
Treatment variables			
Follow-up, months	29.94 ± 24.71	40.98 ± 30.41	0.001
ADT			
CAB	131 (55.1)	363 (55.1)	0.999
Monotherapy	106 (44.9)	296 (44.9)	
Nadir PSA, ng/ml	2.71 ± 10.26	8.51 ± 28.87	0.001
≤0.2	121 (51.1)	139 (21.1)	0.001
≤1.0	172 (72.5)	284 (43.1)	0.001
≤4.0	211 (89.0)	443 (47.2)	0.001
≤10.0	222 (93.7)	551 (63.6)	0.001
Time to nadir PSA, months	11.12 ± 10.55	8.84 ± 11.13	0.001
≤6	95 (40.1)	372 (56.4)	0.001
≤12	164 (69.2)	522 (79.2)	0.001
≤18	200 (84.4)	595 (90.3)	0.009
≤24	222 (93.7)	621 (94.2)	0.780

time to CR was 33.7, 30.53, 26.11 and 24.20 months, respectively ($p < 0.001$). In patients with TTnPSA >6, >12, >18 and >24 months the mean time to CR was 30.16, 38.40, 48.48 and 58.28 months, respectively ($p < 0.001$) (table 5). Although our findings of TTnPSA appear paradoxical, further analysis of data clearly identified the best responders as the group who normalized their PSA (≤4 ng/ml) within the first 6 months of treatment and then continued to lower their PSA levels (table 6). The longer the TTnPSA in this group was, the longer the duration of response was. These patients continued to benefit from hormonal therapy, indicating a continuing hormone responsiveness of their disease. In the absence of PSA normalization within the first 6 months, time to CR was 3 times shorter compared to patients who normalized their PSA. When the patients who progressed were classified according to the duration of response (<24 and >24 months), there was a significant difference in pretreatment PSA, GS, EBI, nPSA and TTnPSA between the groups (table 7).

Factors Influencing nPSA

The mean TTnPSA was 8.84 and 11.12 months in patients with and without progression to CR. Among the 896 initial responders, 603 reached PSA normalization (<4.0 ng/ml) including 260 (29%) with a nadir of <0.2 ng/ml during ADT. These patients were classified according to the median nPSA level achieved (≤1.0 and >1.0 ng/ml) and analyzed for predictive factors such as age, pretreatment PSA, EBI, GS, highest tumor volume in biopsy cores

Table 4. Univariate and multivariate analysis for predictors of CR

	Univariate		Multivariate	
	p	Exp(B)	p	Exp(B)
Age	0.001	0.965	0.125	0.956
Pretreatment PSA, ng/ml	0.001	1.004	–	–
Pretreatment PSA (≤100 vs. >100)	0.001	2.987	0.700	1.210
Extent of bone involvement	0.001	1.103	–	–
EBI (≤10 vs. >10)	0.001	2.263	0.047	2.219
Gleason score	0.002	1.186	–	–
Gleason score (≤7 vs. >7)	0.003	1.568	0.018	0.338
Number of positive cores	0.001	1.145	0.879	0.987
Positive/total cores, %	0.001	1.024	0.014	1.020
Highest tumor volume in biopsy cores, %	0.001	1.023	0.453	1.008
Nadir PSA, ng/ml	0.054	1.010	–	–
Nadir PSA (≤0.2 vs. >0.2)	0.001	3.931	–	–
Nadir PSA (≤1.0 vs. >1.0)	0.001	3.954	0.015	2.737
Nadir PSA (≤4.0 vs. >4.0)	0.001	3.919	–	–
Nadir PSA (≤10.0 vs. >10.0)	0.001	2.906	–	–
Time to nadir PSA, months	0.001	0.982	–	–
Time to nPSA (≤6 vs. >6)	0.001	1.936	0.007	3.134
Time to nPSA (≤12 vs. >12)	0.001	1.690	–	–
Time to nPSA (≤18 vs. >18)	0.009	1.741	–	–
Time to nPSA (≤24 vs. >24)	0.780	1.088	–	–

(%), number of positive biopsy cores, percent positive biopsy cores and TTnPSA. All of these factors except age proved to be significant to predict a nPSA (table 8).

Factors Influencing to Reach PSA ≤4 ng/ml

Univariate and multivariate analysis of the same factors were evaluated to predict PSA normalization (table 9). Pretreatment PSA (≤100 vs. >100 ng/ml), GS (≤7 vs. >7), and EBI (≤10 vs. >10) were statistically significant predictors of PSA normalization in multivariate analysis.

Discussion

ADT has been the standard of care for primary metastatic PC for almost half a century. Although PC is accepted to be an androgen-dependent tumor, the response to ADT primarily depends on patient and disease characteristics (presence and site of metastasis, performance status, pain score, pretreatment PSA, GS, etc.).

Initial Response to ADT

Patients with PC who had metastasis to the bones at the time of diagnosis were the focus of this study. An initial response to ADT by our study criteria was observed in more than 90% of the patients and interestingly two thirds of the patients achieved PSA levels ≤4 ng/ml and almost half of the patients had levels of PSA ≤1 ng/ml. Large-scale studies are limited in this respect however.

Table 5. Duration of response according to PSA cut-off values and time to nPSA in patients with CR

	Duration of response, months	p value*
Number	659	
Nadir PSA, ng/ml		
≤0.2 vs. >0.2	33.77 ± 23.57 vs. 19.40 ± 18.22	0.001
≤1.0 vs. >1.0	30.53 ± 23.99 vs. 16.27 ± 14.20	0.001
≤4.0 vs. >4.0	26.11 ± 21.80 vs. 14.84 ± 14.13	0.001
≤10.0 vs. >10.0	24.20 ± 20.65 vs. 13.35 ± 15.65	0.001
Time to nadir PSA, months		
≤6 vs. >6	16.48 ± 16.91 vs. 30.16 ± 21.74	0.001
≤12 vs. >12	18.24 ± 17.48 vs. 38.40 ± 22.40	0.001
≤18 vs. >18	19.63 ± 17.19 vs. 48.48 ± 27.60	0.001
≤24 vs. >24	20.21 ± 17.16 vs. 58.28 ± 31.30	0.001

* Student's t test.

Table 6. Correlation between response duration and PSA normalization (≤4 ng/ml) attained within the first 6 months of therapy and time to the lowest level of PSA (nadir) ever achieved

Time to nadir PSA, months	Duration of response, months			Time from nPSA to CRPC, months		
	PSA ≤4 ng/ml within 6 months of treatment	PSA >4 ng/ml within 6 months of treatment	p*	PSA ≤4 ng/ml within 6 months of treatment	PSA >4 ng/ml within 6 months of treatment	p*
≤6	21.58 ± 21.12	9.64 ± 9.13	0.0001	16.76 ± 19.08	6.56 ± 9.34	0.0001
>6	32.50 ± 17.42	24.16 ± 17.09	0.004	18.05 ± 9.84	6.91 ± 7.81	0.0001
≤12	21.71 ± 20.51	11.65 ± 10.70	0.0001	16.68 ± 18.56	6.62 ± 9.32	0.0001
>12	40.46 ± 18.92	33.69 ± 17.76	0.118	20.09 ± 10.51	7.05 ± 5.06	0.0001
≤18	22.29 ± 20.32	13.12 ± 11.72	0.0001	16.86 ± 18.20	6.70 ± 9.11	0.0001
>18	55.20 ± 21.51	40.81 ± 20.41	0.079	22.50 ± 6.35	6.60 ± 3.61	0.0001

CRPC = Castration-resistant prostate cancer. * Between the subgroups for PSA value after 6 months from ADT initiation.

Table 7. Patient disease characteristics according to duration of response (time to CR)

	Duration of response		p value
	<24 months	≥24 months	
Number	426 (64.6)	233 (35.4)	
Pretreatment PSA, ng/ml	288.61 ± 695.39	173.60 ± 577.64	0.026
<20	47 (11.0)	40 (17.2)	0.012
20–100	170 (39.9)	100 (42.9)	
>100	209 (49.1)	93 (39.9)	
Extent of bone involvement	8.31 ± 4.12	7.13 ± 4.35	0.001
≤10	124 (29.8)	98 (43.8)	0.001
>10	292 (71.2)	126 (56.2)	
Gleason score	7.87 ± 1.28	7.37 ± 1.46	0.001
<7	39 (9.5)	55 (24.7)	0.001
7	129 (31.6)	68 (30.5)	
>7	241 (58.9)	100 (44.8)	
Nadir PSA, ng/ml	11.63 ± 35.05	2.88 ± 8.72	0.001
<0.2	48 (11.2)	91 (39.1)	0.001
0.2–1.0	82 (19.3)	63 (27.0)	
>1.0	296 (69.5)	79 (33.9)	
Time to nadir PSA, months	5.39 ± 3.98	15.03 ± 16.10	0.001
<6	289 (67.9)	83 (35.6)	0.001
6–12	103 (24.2)	41 (17.6)	
>12	34 (7.9)	109 (46.8)	

Hussain et al. [8] reported PSA levels of ≤4.0 ng/ml in 81.3% and undetectable PSA (0.2 ng/ml) in 48% of their patients receiving ADT after the first 6–7 months.

In a smaller study, Collette et al. [9] suggested that in patients with painless metastatic PC (n = 252, 99.3% had bone metastasis) also with favorable prognostic factors, 65% achieved a PSA of ≤10 ng/ml and 20.2% had a value of PSA ≤1 ng/ml after initiation of ADT. More recently, Collette et al. [10] reported a 90.0% response rate (decrease in PSA by ≥50% from baseline PSA) and 49.8% PSA normalization (≤4 ng/ml) in 763 assessable patients.

In a retrospective analysis of data from 92 patients with bone metastasis at the time of diagnosis, Sim et al. [11] observed that 62% attained a nPSA level (overall re-

Table 8. Factors influencing nPSA in group of responders to ADT initially

	nPSA ≤1 (%)	nPSA >1 (%)	p value
Number	455 (50.5)	441 (49.5)	
Age	67.88 ± 8.45	68.40 ± 7.83	0.324
Pretreatment PSA, ng/ml	145.02 ± 519.12	261.16 ± 615.66	0.001
≤100	321 (70.5)	182 (41.3)	0.001
>100	134 (29.5)	258 (58.7)	
Extent of bone involvement	6.34 ± 4.59	8.48 ± 3.94	0.001
≤10	196 (52.6)	134 (31.6)	0.001
>10	177 (47.4)	290 (68.4)	
Gleason score	7.33 ± 1.42	7.89 ± 1.33	0.001
≤7	241 (58.2)	178 (41.1)	0.001
>7	173 (41.8)	255 (58.9)	
Number of positive cores	5.45 ± 2.71	7.02 ± 2.93	0.001
Positive/total cores, %	71.41 ± 27.93	85.22 ± 21.81	0.001
Highest tumor volume in biopsy cores, %	74.78 ± 25.51	82.95 ± 17.21	0.005
Time to nadir PSA, months	11.12 ± 12.53	8.07 ± 11.68	0.001
≤6	198 (44.2)	266 (60.7)	0.001
>6	251 (55.8)	173 (39.3)	

Table 9. Factors influencing PSA normalization

	Univariate		Multivariate	
	p	Exp(B)	p	Exp(B)
Age	0.026	0.981	0.797	0.993
Pretreatment PSA, ng/ml	0.001	1.000	–	–
Pretreatment PSA (≤100 vs. >100)	0.001	5.038	0.001	10.406
Extent of bone involvement	0.001	1.208	–	–
EBI (≤10 vs. >10)	0.001	4.872	0.019	2.718
Gleason score	0.001	1.408	–	–
Gleason score (≤7 vs. >7)	0.001	2.150	0.008	2.921
Number of positive cores	0.001	1.130	0.378	0.923
Positive/total cores, %	0.001	1.023	0.184	1.011
Highest tumor volume in biopsy cores, %	0.001	1.028	0.471	1.009
Time to nadir PSA, months	0.058	0.986	–	–
Time to nadir PSA (≤6 vs. >6 months)	0.001	1.629	0.311	1.494

sponse rate; definition of response is unknown) and 25% reached a nadir of <2 ng/ml. Response rates from different series were summarized in their table 10.

There is no consistency in response rates to ADT among various investigations basically due to the definition of the response to ADT, and possibly patient and disease characteristics such as pretreatment PSA, percentage of GS ≥8, painless bone metastasis, performance status ≤1, burden of the bone involvement, and distribution of age. In our study, only initial PSA and EBI were independent predictors of response to ADT.

Factors Influencing nPSA

Kwak et al. [12] found GS and initial PSA influencing nPSA in a heterogeneous setting (stage C and D patients). In a series of 177 men with stage C or D PC (123 men with stage D cancer), 36 patients (29.3%) had a nPSA <0.2 ng/ml and 63 patients (51.2%) had nPSA <1 ng/ml. These results were very similar to our findings of 29.0 and 50.8% respectively in our patients for the same nPSA levels. Benaim et al. [13] reported that the patients with a higher GS had significantly higher nadir values than did those with moderate and low-grade tumors. In contrast, they

demonstrated that nPSA has no correlation with initial PSA or TTnPSA. We determined initial PSA, EBE, GS, the highest tumor volume in biopsy cores, percent positive cores and TTnPSA as the predictors of a nPSA level ≤1.0 ng/ml. Also, there was a 4-fold increase in unresponsiveness to ADT in patients with a GS of 8–10 compared to GS ≤6.

Factors Influencing to Reach PSA ≤4 ng/ml

Although their definition of response and time to nPSA were different, Hussain et al. [8] observed that higher PSA, GS ≥8, younger age, poor performance status, and presence of bone pain were independent predictors of failure to achieve of a PSA of ≤4 ng/ml at months 6 and 7. They also reported the status of achieving PSA of ≤4.0 ng/ml after 7 months ADT as a strong and specific predictor of risk of death. We detected an initial PSA of ≤100 ng/ml, GS ≤7 and EBI ≤10 foci were predictors of PSA normalization on multivariate analysis.

Predictors of CR and Duration of Response

PSA and initial Gleason grade were reported as the most important predictors of the time to androgen independence in locally advanced PC [13]. These findings were further corroborated by Kwak et al. [12] who reported that pretreatment PSA, PSA at 6 months after treatment and bone metastasis were significantly associated with progression to castration-resistant PC. In another study, Dijkman et al. [14] reported early normalization of PSA was shown to predict and improved long-term response to hormonal therapy in terms of CR and death. Our data indicate that approximately a quarter of the patients respond favorably to ADT with a longer failure-free period while the rest succumb to CR within a median of 12–18 months. nPSA level (≤1.0 vs. >1.0 ng/ml), TTnPSA (≤6 vs. >6 months), percent positive core, GS (≤7 vs. >7), and EBI (≤10 vs. >10) were all statistically significant factors for the prediction of CR in multivariate analysis. In terms of progression to CR the most favorable group were the patients with a nPSA ≤0.2 ng/ml (33.7 months) and TTnPSA >24 months (the mean time to CR of 58.28 months) (table 5). Early (within 6 months) normalization of PSA and a continuing response to hormonal therapy with progressive decline in PSA levels resulting in a longer TTnPSA defines the best prognostic group. These patients had an average of more than 7 years from the initiation of treatment until the emergence of CR (table 6). An intermediate group may be defined as those who did not normalize their PSA within 6 months but continue to lower their PSA, indicating a longer TTnPSA. However, progression to CR in this group of patients was not different than those with much shorter TTnPSA. In this study, predictors of duration of response more than 2 years were pretreatment PSA, GS, EBI, nPSA and TTnPSA (table 7).

Limitations of the Study

The limitations of our analysis are discussed below. It is retrospective in design and the model developed a low standardization as a result of using multicenter data. Patients enrolled in this study were from a relatively long period of time (1989–2008). Changes in the technique of prostate biopsy certainly took place during this period as to the number and site of biopsy cores. Therefore the number of cores and site of biopsy cores were not uniform. Thus we are unable to evaluate the effect of these variables on pathological evaluation of biopsy specimens. During this period there were also changes in pathological evaluation of specimens with the accumulation of experience. Other factors such as pain score and PSA doubling time, previously reported as predictive factors for survival in metastatic PC, were not assessed in this analysis. Despite these limitations, our cohort was uniform in terms of newly diagnosed primary advanced PC with bone metastasis without any previous treatment with a large size.

Conclusion

The results of this study indicate that it is possible to predict the initial response to ADT by pretreatment PSA levels and EBI, while the duration of response can be reflected by a multitude of clinical factors including nPSA, TTnPSA, percent positive cores, biopsy GS and EBI. Thus, using readily available clinical data in primary metastatic PC patients, it seems to be possible to provide a better estimation of response to treatment and time to failure in a particular patient allowing better counseling with the consequence of additional or experimental treatment suggestions in case of a high probability of a dismal response to initial ADT.

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