Cutoff value of time to prostate-specific antigen nadir is inversely correlated with disease progression in advanced prostate cancer

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Abstract

To identify the early predictor of progression to castration-resistant prostate cancer (CRPC) for different stage of advanced PC patients, we focused on time to prostate-specific antigen (PSA) nadir following primary androgen deprivation therapy (PADT). We reviewed 184 advanced (locally advanced and metastatic) PC patients (101 patients with bone metastasis (BM) and 83 patients without BM at presentation) who had received PADT at our institution. We evaluated laboratory data, pathological results, and the influence of PSA kinetics impact on disease progression. The progression rates were analyzed with reference to the nadir PSA level and time to PSA nadir (TTN) following PADT by Kaplan–Meier method. In all, 103 patients (56%) progressed to CRPC. Nadir PSA lower than 0.2 ng/ml (nadir ≤ 0.2) during PADT was observed in 114 patients (62%). Median TTN was 8.5 months in patients with BM and 11.5 months in patients without BM. Multivariate analysis revealed that nadir ≤ 0.2 following PADT ($P < 0.001$), longer TTN (> 8 months) ($P < 0.001$), extent of disease on bone scan grade ($P = 0.02$), and T stage ($P = 0.04$) in BM group and nadir ≤ 0.2 following PADT ($P < 0.001$), longer TTN (> 11 months) ($P < 0.001$), and T stage ($P = 0.03$) in without BM group were independent prognostic factors for progression. In both groups, longer TTN identified patients with prolonged progression-free survival in both nadir ≤ 0.2 and > 0.2 nadir levels. Longer TTN is strongly associated with a low risk of disease progression, and the cutoff value of TTN could be inversely correlated with disease progression.

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Introduction

The standard initial systemic therapy for advanced prostate cancer (PC) is androgen deprivation therapy (ADT). Even PC patients with metastatic disease initially respond well to hormone therapy but then progress to castration-resistant PC (CRPC), which is accompanied with high mortality rate (Eisenberger & Carducci 2007).

Several clinical and laboratory data have been proposed as prognostic factors for predicting survival including performance status, T stage, serum alkaline phosphatases, hemoglobin, and testosterone levels (De Voogt *et al.* 1989, Ishikawa *et al.* 1989). The J-CAPRA score is a novel, validated score for predicting outcomes among patients undergoing primary ADT (PADT) across the full spectrum of risk and stage,

including advanced disease (Cooperberg *et al.* 2009). Nadir prostate-specific antigen (PSA) level after hormone therapy has been reported as an important tool to predict progression in patients with metastatic PC (Matzkin *et al.* 1992, Kwak *et al.* 2002). Recently, combination of lower PSA nadir level and longer time to PSA nadir (TTN) after hormone therapy is associated with longer progression-free and overall survival in metastatic PC patients (Morote *et al.* 2004, Choueiri *et al.* 2009, Hori *et al.* 2011, Huang *et al.* 2011a,b). However, these studies included various clinical stages and patients with different types of pre-treatment such as radical prostatectomy or radiotherapy. We have also demonstrated that the combination of lower PSA nadir (lower than 0.2 ng/ml) and longer TTN (more than 9 months) during initial

hormone therapy is the most important early predictors for overall survival for advanced PC patients with bone metastasis (BM) at diagnosis (Sasaki et al. 2011).

In this study, we focused on the TTN following PADT and analyzed the difference between two advanced PC groups (with or without BM at presentation). The ability to predict which patients are more likely to develop early CRPC could be helpful when choosing the best treatment strategy.

Materials and methods

A retrospective study was conducted in 184 advanced (locally advanced and metastatic) PC patients. One hundred and one patients were with BM and 83 patients were without BM at presentation, who had received PADT at our institution from January 2000 to October 2011 (no one with disease recurrence after local treatment was included). All patients received PADT with LHRH agonist or surgical castration accompanied with an antiandrogen (combined androgen blockade) and were followed at our hospital every 4 weeks. The antiandrogen, either flutamide or bicalutamide, was used initially. The extent of bone metastases (extent of disease on bone scan (EOD) grade) was graded as follows: 1 (fewer than six hot spots), 2 (between six and 20 hot spots), 3 (>20 hot spots), or 4 (super scan pattern or >75% involvement of skeleton) (Soloway et al. 1988). PSA was serially measured every 4 weeks during PADT treatment. Disease progression (PADT failure) was determined by exponentially increasing PSA at three time points that were measured every 4-week interval, and progression-free survival was calculated from the day of the initiation of PADT until the date correspond to the day that the increase was first observed (Japanese Urological Association 2001). The disease progression rate was analyzed in terms of the nadir PSA (the lowest PSA level during PADT) and TTN. TTN was defined as the duration time from the initiation of PADT to the date that the lowest PSA value was first recorded (Kwak et al. 2002).

PSA nadir level was categorized into ≤ 0.2 and > 0.2 ng/ml, a cutoff point that has been previously correlated with disease progression (Morote et al. 2004, Huang et al. 2011a). The optimal cutoff point of TTN has not been determined, as previously reported cutoff points of TTN were derived from PC patient with heterogeneous background, such as various clinical stages and different types of pretreatment. Therefore, we selected median value of TTN as an optimal threshold. The median TTN was 8.5 months in patients with BM and 11.5 months in patients

without BM. PSA reduction rate after PADT (%) was calculated as follows: $100 \times (\text{initial PSA} - \text{nadir PSA}) / \text{initial PSA}$.

Multivariate analysis was performed according to the Cox proportional hazards regression model. Only the variables found to be significant on univariate analysis ($P < 0.05$) were entered into the multivariate analysis. The progression rate was calculated with the Kaplan–Meier method. Bonferroni correction was used in pairwise comparison with the progression significance level of 0.05. The statistical analysis was undertaken using SAS software, version 8.2 (SAS Institute, Cary, NC, USA), and $P < 0.05$ was considered to be statistically significant. An institutional review board of our hospital approved this study.

Results

Clinical characteristics of the patients in this study are shown in Table 1. Median age at diagnosis was 74.5 (56–89) years, and median follow-up was 41.3 (range

Table 1 Patients characteristics

Number of patients	184
Without bone metastasis	83
With bone metastasis (%)	101
EOD grade	
1	49 (49)
2	29 (29)
3	18 (18)
4	5 (5)
Median age at diagnosis (range)	74.5 (56–89) years
Median initial PSA (range)	102.4 (6.0–12 700) ng/ml
Median nadir PSA (range)	0.2 (0.004–1310) ng/ml
Median time to PSA nadir (range)	9.6 (1.0–88) months
Clinical stage at diagnosis (%)	
T3b/T4/N1	72 (39)
M1	112 (61)
PS (%)	
0	157 (86)
1	19 (9.5)
2	1 (0.5)
3	5 (3)
4	2 (1)
Gleason score (%)	
≤ 6	31 (16.5)
7	71 (38.5)
≥ 8	82 (45)
Type of ADT (%)	
LHRH analog with antiandrogen	91 (49)
Surgical castration with antiandrogen	93 (51)

EOD, extent of disease on bone scan; PSA, prostatic specific antigen; PS, performance status; ADT, androgen deprivation therapy.

Table 2 Univariate and multivariate analysis of factors predicting progression-free survival in without bone metastasis ($n=83$)

Factors	Univariate Hazard ratio (95% CI) (P value)	Multivariate Hazard ratio (95% CI) (P value)
Age (<75 vs ≥ 75)	2.10 (1.07–4.15) (0.03)	1.46 (0.72–2.92) (0.28)
Initial PSA (≥ 100 vs <100)	1.56 (0.79–3.06) (0.19)	–
Nadir PSA (>0.2 vs ≤ 0.2)	9.57 (4.74–19.3) (<0.001)	24.6 (9.62–62.8) (<0.001)
Time to PSA nadir (≤ 11 m vs >11 m)	3.64 (1.84–7.20) (<0.001)	4.60 (1.97–10.7) (<0.001)
PS (1, 2, 3, 4 vs 0)	3.39 (0.99–11.6) (0.051)	–
Gleason score (≥ 8 vs <8)	1.42 (0.72–2.79) (0.30)	–
T ($\geq 3b$ vs <3b)	4.35 (1.50–12.6) (0.006)	3.49 (1.06–11.4) (0.03)
N (1 vs 0)	1.46 (0.76–2.79) (0.24)	–
Hb (<12 vs ≥ 12)	1.64 (0.63–4.25) (0.30)	–
Alb (<4 vs ≥ 4)	1.27 (0.55–2.91) (0.56)	–
LDH (≥ 250 vs <250)	1.19 (0.46–3.08) (0.70)	–

PS, performance status; Hb, hemoglobin; Alb, albumin; LDH, lactate dehydrogenase.

1–141) months. One hundred and three patients (56%) progressed to PADT failure.

The univariate analysis and multivariate analysis of factors predicting progression-free survival were shown in Tables 2 and 3. In without BM group, multivariate analysis revealed that lower PSA nadir following PADT ($P<0.001$), longer TTN (>11 months) ($P<0.001$), and T stage ($P=0.03$) were independent prognostic factors for progression. In with BM group, multivariate analysis revealed that lower PSA nadir following PADT ($P<0.001$), longer TTN (>8 months) ($P<0.001$), EOD grade ($P=0.02$), and T stage ($P=0.04$) were independent prognostic factors for progression.

The progression-free rates were estimated by the Kaplan–Meier method for comparison between with and without BM group. The median values of progression-free rates in with and without BM group were 13.2 and 29.3 months respectively ($P<0.001$).

Progression-free rates at 5 years in with and without BM group were 20.9 and 51.3% respectively. Significant difference was observed between the two groups ($P<0.001$; Fig. 1).

In order to investigate the interaction between PSA nadir and TTN, we performed combined analyses of PSA nadir and TTN, in both with and without BM group (Figs 2 and 3). In without BM group, significant differences were seen in disease progression between TTN ≤ 11 months and TTN >11 months in both nadir ≤ 0.2 and >0.2 groups ($P=0.01$ and $P<0.001$ respectively) (Fig. 2). In with BM group, significant differences were seen in disease progression between TTN ≤ 8 months and TTN >8 months in both nadir ≤ 0.2 and >0.2 groups ($P=0.009$ and $P<0.001$ respectively) (Fig. 3).

Median reduction rate of PSA after PADT was 99.8% (87.2–99.9) and 99.8 (0–99.9) in without and

Table 3 Univariate and multivariate analysis of factors predicting progression-free survival in with bone metastasis group ($n=101$)

Factors	Univariate Hazard ratio (95% CI) (P value)	Multivariate Hazard ratio (95% CI) (P value)
Age (<75 vs ≥ 75)	1.04 (0.66–1.63) (0.86)	–
Initial PSA (≥ 100 vs <100)	1.61 (0.95–2.72) (0.07)	–
Nadir PSA (>0.2 vs ≤ 0.2)	3.99 (2.46–6.46) (<0.001)	5.45 (2.94–10.0) (<0.001)
Time to PSA nadir (≤ 8 m vs >8 m)	4.27 (2.65–6.88) (<0.001)	4.45 (2.50–7.90) (<0.001)
PS (1, 2, 3, 4 vs 0)	1.99 (1.15–3.44) (0.01)	1.31 (0.63–2.74) (0.45)
Gleason score (≥ 8 vs <8)	1.50 (0.95–2.36) (0.07)	–
EOD grade (3, 4 vs 1, 2)	2.80 (1.66–4.72) (<0.001)	2.10 (1.10–4.00) (0.02)
T ($\geq 3b$ vs <3b)	2.22 (1.29–3.80) (0.003)	1.84 (1.00–3.36) (0.04)
N (1 vs 0)	1.54 (0.94–2.52) (0.08)	–
Hb (<12 vs ≥ 12)	2.06 (1.19–3.55) (0.008)	1.73 (0.86–3.48) (0.12)
Alb (<4 vs ≥ 4)	2.42 (1.51–3.88) (<0.001)	1.26 (0.71–2.24) (0.42)
LDH (≥ 250 vs <250)	1.98 (1.16–3.36) (0.01)	0.70 (0.35–1.42) (0.32)

PS, performance status; EOD, extent of disease on bone scan; Hb, hemoglobin; Alb, albumin; LDH, lactate dehydrogenase.

Figure 1 Comparison of the progression-free survival between advanced PC patients without BM (solid line) and with BM (dotted line).

with BM group respectively. No significant difference was observed between two groups.

Discussion

PADT is generally performed and effective for advanced PC; however, some patients become CRPC. Once CRPC come into existence, patients will die within 3 years (Eisenberger & Carducci 2007). Our aim was to find more reliable early prognostic factors in advanced PC patients before or during initial hormone therapy. We believe that it could be useful for decision making of the best treatment strategy to predict which patients are more likely to develop early progression to CRPC.

Prognostic factors for PC have been evaluated, with initial PSA, Gleason score, and clinical stage generally regarded as the prognostic factors for progression after PADT including full spectrum of risk and stage (Cooperberg et al. 2009). We evaluated the prognostic factors for progression in different PC stage (with or without BM). Our results demonstrate that T stage, lower PSA nadir, and longer TTN are independent prognostic factors for disease progression in both groups, and EOD grade is also an independent prognostic factor in with BM group (Tables 2 and 3).

It is generally considered that rapid reduction of PSA would correlate with more PC cell death followed by higher survival and shorter TTN correlated with longer remission periods (Arai et al. 1990), whereas it is recently reported that longer TTN is associated with longer progression-free survival (Morote et al. 2004, Hori et al. 2011, Huang et al. 2011a). This finding seems counterintuitive.

As for progression, Morote et al. reported that a PSA nadir ≤ 0.2 ng/ml and TTN ≥ 12 months was

associated with a low risk of PSA progression with metastatic PC patients (Morote et al. 2004). Hori et al. (2011) have reported that PSA nadir < 1 ng/ml and TTN > 12 months associated with low risk of biochemical relapse in BM patients, and PSA nadir < 0.1 ng/ml and TTN > 24 months associated with low risk of biochemical relapse in without BM patients. The limitation of their studies could be the patient's classification. Their patients were stratified in two groups by PSA nadir level or TTN. Inadequate PSA responders with shorter TTN due to a little PSA decline from high level of PSA, which is obviously associated with poor progression, might possibly be included in shorter TTN group. Interestingly, Huang et al. stratified in four groups by combination PSA nadir level and TTN. They demonstrated that PSA nadir ≥ 0.2 ng/ml and TTN < 10 months had significant shorter time to disease progression for advanced or metastatic patients. However, their study did not demonstrate that prolonged TTN was correlated with longer progression-free survival in adequate PSA responders (PSA nadir ≤ 0.2) because of including various clinical stages and patients with different types of pretreatment such as radical prostatectomy or radiotherapy (Huang et al. 2011a).

We found that TTN in patients without BM is significantly longer than those with BM. In addition, most important finding in this study is that in both advanced PC patients with and without BM groups, longer TTN identified patients with prolonged progression in both groups with PSA nadir ≤ 0.2 and > 0.2 . We propose that the optimal cutoff value of TTN is > 11 months in advanced PC patients without BM and > 8 months in those with BM. Taken together, a rapid decrease in PSA expression during ADT strongly indicates more aggressive disease, and by

Figure 2 Stratification of progression-free survival by PSA nadir and TTN in without BM group.

Figure 3 Stratification of progression-free survival by PSA nadir and TTN in with BM group.

contrast, prolonged TTN is associated with low risk of progression.

So far, the mechanism of this clinical observation remains unknown. We speculate about the possible explanations. First androgen-depletion of androgen-dependent PC cells results in early G1 arrest characterized by reduced cyclin-dependent kinase activity and unphosphorylated retinoblastoma tumor suppressor protein (Knudsen *et al.* 1998). There might exist two types of PC cells: one has the character of differentiating to CRPC during cell cycle arrest with rapid reduction of PSA induced by ablation of androgen receptor and the other gradually goes to apoptosis (cell death) after cell cycle arrest with slow reduction of PSA. The former would be rich in shorter TTN group, and the latter is rich in longer TTN group. Second hormone-resistant PC cells, which are PSA producing, can grow in low androgen environment and would be originally present in a large number in advanced PC patients. A PC cell line that displays these characteristics (PSA-producing and androgen independent) is available for experimental research (Yeung *et al.* 2000, Onishi *et al.* 2001). Third PSA or unknown factor produced by androgen-dependent PC cells might play a role of inhibiting the growth of androgen-independent PC cells, thus an adequate environment for growing androgen-independent PC cells might be induced by a rapid removal of androgen-dependent PC cells. Further *in vitro* and *in vivo* experiments about androgen independency and interaction between androgen-dependent and androgen-independent PC cells are required to confirm these hypotheses.

Andriole *et al.* examined the effect of 5 α -reductase inhibitor dutasteride on the incidence of PC. They

found that dutasteride reduced the risk of incident PC; however, detection of Gleason 8–10 PC was significantly higher in the dutasteride group than in the placebo group (Andriole *et al.* 2010). This finding might support our third hypothesis stated earlier.

Based on our data and hypothesis, intermittent ADT might be one of the ideal hormone therapy strategy for preventing the progression to CRPC, as longer TTN could be obtained by intermittent ADT. Randomized studies completed to date indicate that intermittent ADT might be equivalent to continuous ADT (Calais da Silva *et al.* 2009). However, randomization criteria for this trial is a PSA decline of 80%, or to <4 ng/ml, on initial 3-month continuous ADT. Earlier start of intermittent ADT might prolong TTN followed by good prognosis.

We recognize the limitations of a retrospective study that includes a relatively few cases. However, we believe that further prospective studies with large cohort size and basic research about progression to CRPC are required to confirm our findings.

Conclusion

In this study, we have demonstrated that the cutoff value of TTN following PADT for predicting progression is inversely correlated with disease progression in PC patients. The optimal cutoff value of TTN for predicting low risk of progression might be TTN > 8 months in advanced PC patients with BM and TTN > 11 months in those without BM regardless of nadir PSA levels.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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