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The Use of PSA Doubling Time to Predict Prognosis and the Use of PSA Response to Assess the Success for Prostate Cancer Patients Undergoing Docetaxel Chemotherapy

Sarp K. Keskin[1*], Asif Yildirim[2], Cengiz Canakci[2], Ismail Ulus[2], Ramazan Gokhan Atis[2], Turhan Caskurlu[2]

[1]Department of Urology, The University of Texas MD Anderson Cancer Center, Houston, USA
[2]Department of Urology, The University of Istanbul Medeniyet, Goztepe Training and Research Hospital, Istanbul, Turkey
Email: *skkeskin@mdanderson.org

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Abstract

In the targeted therapy era, it is critical to know the certain points to start or discontinue chemotherapy for patients with castration resistant metastatic prostate cancer. The prognostic factors to determine this response are still not clear yet. We tried to find out if the PSA doubling time helps us to predict the patients who will benefit from docetaxel chemotherapy most, and also to question the value of the PSA response to chemotherapy. Retrospectively, 70 patients who had hormone refractory metastatic prostate cancer that were given at least 4 cycles of docetaxel chemotherapy between 2002 and 2015 were evaluated. After the onset of docetaxel, PSA response to therapy and overall survival rates were analyzed to figure out if these parameters were related to PSA doubling time. The only statistically significant prognostic parameter affecting overall survival was the best PSA response rate to docetaxel chemotherapy being over or under 50%. The most significant parameter that affects the PSA doubling time was the clinical stage at the time of diagnosis. PSA doubling time is not a useful predictive tool for predicting response to docetaxel. By means of overall survival, the clinical stage at the time of diagnosis was the best predictive tool for our cohort. The best PSA response rate to docetaxel chemotherapy was found to be a valuable parameter. The study being retrospective and the low number of patients included in this cohort can be the main weaknesses of this study. Further studies to determine which other factors can be useful are needed.

*Corresponding author.

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Keywords

Castration Resistant Prostate Cancer, Docetaxel, PSA Doubling Time, PSA Kinetics, Chemotherapy

1. Introduction

Prostate cancer is the most common visceral malignancy amongst men in the US [1]. In addition, it is the most common solid cancer and the most common cause of death due to cancer in European men [2]. Nowadays most of the patients are getting diagnosed as localized prostate cancer [3]. With contemporary treatment options, the overall survival for this group of patients is over 90% [4] [5]. Men with localised disease can have very different treatment options, ranging from observation alone through to radical surgery, for each individual patient.

For those who have metastatic prostate cancer, the most common first line treatment option is androgen deprivation therapy (ADT). The survival of patients with metastatic prostate cancer progressing on ADT (castration-resistant prostate cancer) has improved substantially. In addition to docetaxel, which has been used for over a decade, new drugs have shown efficacy with improvements in overall survival leading to licensing for the treatment of metastatic castration-resistant prostate cancer (CRPC). Because of these recent changes in the therapeutic landscape, no vigorous data is available to inform on the selection of patients for a specific treatment for CRPC [6] [7]. With the developments in the last decade, we now have many options for hormone refractory metastatic prostate cancer patients like newer generation chemotherapeutics, targeted therapies, vaccines, immune checkpoint inhibitors [8]-[11].

Docetaxel (DX) is one the first cytotoxic therapeutics associated with a survival benefit in CRPC and the most commonly used chemotherapeutic in hormone refractory metastatic prostate cancer patients in the last decade [12]. Because it is an effective therapy, docetaxel is likely to remain an important part of the treatment arsenal against metastatic prostate cancer for the foreseeable future, despite its toxicities and limitations. Every patient represents a unique response to this therapy. In addition, there is no commonly accepted parameter that can be used to predict the response rate or time to chemotherapy. We tried to find out one using the PSA doubling time (PSA-DT).

2. Materials and Methods

Seventy patients with castration resistant prostate cancer, who received ADT as first line, and after failure of this therapy, initiated to chemotherapy and received at least 4 cycles of docetaxel at our clinic between 2002 and 2015 were respectively evaluated. Patient characteristics were presented at **Table 1**.

Table 1. The demographic and clinical findings of patients.

	Number	Minimum	Maximum	Average	Standart Deviation
Age	70	52	82	69.16	8.34
Gleason Score	70	4	10	7.34	1.20
Trus-%	70	40	100	86.14	16.26
Clinical Stage	70	1	4	2.47	0.60
Body Mass Index	70	21	30	25.19	2.42
First PSA (ng/ml)	70	2.86	6013	317.25	948.43
ADT (months)	70	6	156	42.16	31.53
ADT PSA nadir(ng/ml)	70	0.01	159	6.09	21.18
Time to get PSAn with ADT (months)	70	2	55	13.44	10.18
PSA - DT (days)	70	15	317	83.96	57.44
PSA-V (ng/ml/month)	70	0.03	310	19.31	42.07
Last PSA before DX	70	19	2499	258.82	525.96
DX cures	70	4	23	7.36	4.6
Follow Up Time (months)	70	5	70	22.27	13.829

Median time of follow-up was calculated using the reverse Kaplan-Meier method.

The performance status of the patients before chemotherapy was measured by the Eastern Cooperative Oncology Group (ECOG) performance scale [13]. Patients with score 3 and higher were not included.

All the patients received androgen deprivation therapy (ADT) before DX chemotherapy. The PSA-nadir (PSAn) level under ADT was evaluated in two groups (≤4 ng/ml and >4 ng/ml).

The PSA-DT was calculated by evaluating all the PSA values between the onset of DX chemotherapy and the PSAn level while receiving ADT. PSA values included were all seen in the last 3 months before the onset of DX chemotherapy.

We used to calculate PSA-DT was the Memorial Sloan Kettering nomograms. To be specific, PSA-DT was calculated by natural log of 2 (0.693) divided by the slope of the relationship between the log of PSA (P_1, P_2) and time of PSA (T_1, T_2) measurement for each patient. $T = (t_2 - t_1)\log(2)/\log(P_2/P_1)$ [14].

The literature evaluation for the PSA-DT showed us that the most used cut-off values were 45 and 70 days [15] [16]. Therefore, we calculated the patients PSA-DT values by using these two cut-off days. We also grouped the patients by their PSA level on diagnosis (<7 ng/ml, =7 ng/ml, >7 ng/ml).

All included patients who had castration resistant prostate cancer (CRPC) had 75 mg/m^2 DX chemotherapy every 21 days. The PSA response to DX was evaluated in three groups (PSA decrease, <30%, 30% - 50%, >50%)

Statistical Analysis

Within the cohort, the Cox proportional hazards model was used to model the overall survival. Multiple cause-specific Cox regression models were carried out to associate PSA kinetics. The Cox regression models included age, WHO histopathological grade and either the last PSA before onset of DX PSA or the most recent PSA measurement available. Results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs).

3. Results

Age of the included patients was between 59 and 82 (average, 69). The median Gleason score was 7.34 and the tumor rate at the diagnostic biopsy was 86%. The PSA level at the time of diagnosis was between 2.8 ng/ml and 6013 ng/ml (average 317.25 ng/ml).

All the patients received ADT before DX chemotherapy. The PSAn level under ADT was evaluated in two groups (≤4 ng/ml and >4 ng/ml). According to this, 77% of the patients had PSAn levels under 4 ng/ml. The time to reach the PSAn level was over 6 months in the 87% of all patients.

Before DX chemotherapy, 28.6% of the patients had a PSA-DT under 45 days, 21.8% had PSA-DT between 45 and 70 days, and 48.6% had a PSA-DT over 70 days. Statistical analysis of these groups showed no significant correlation with survival rates.

We evaluated two possible factors that affect PSA-DT. These were Gleason score and clinical stage at the time of diagnosis. None of these two parameters showed statistically significant correlation with survival or PSA response rates. However, the stage at the time of diagnosis was related to the PSA-DT. Clinically T3 and T4 patients had significantly lower PSA-DT (**Table 2**, **Table 3**).

The PSA response rate (PSA-R) was calculated as the ratio of the lowest PSA level under DX chemotherapy (PSAndx) to the last PSA level before DX chemotherapy (PSAa). (PSA-R = PSAa/PSAndx)

The group of patients who had PSA-R < 50%, had significantly lower survival rates ($p = 0.049$). The median overall survival time was 21.37 months for these patients. On other hand, the >50% PSA-R group had 33.23 months of median overall survival. These findings are shown in the **Table 4**.

4. Discussion

To predict the survival rates and response rates to chemotherapy for metastatic and castration resistant prostate cancer is not possible to our knowledge. We investigated our database to find out a prognostic factor that may be useful for predicting the prognosis of patients who are under docetaxel chemotherapy.

This may also be helpful to designate a cut-off value for making an extra move for therapy. The initial PSA levels differ a lot from patient to patient. This is because of the variable PSA expression of tumors and also the heterogeneity of the tumor cells [17].

One of the first studies about PSA-DT was published in 2001. At this study, a group considered to show a good prognosis (T1b or T2b, N0, M0, Gleason score < 7, PSA < 15 ng/ml) was evaluated and PSA-DT was

Table 2. PSA-DT according to gleason scores.

PSA-DT cutoff 75 days	Gleason Score			Total	p
	<7	7	>7		
PSA-DT ≤ 75 days	7	18	11	36	
PSA-DT >75 days	8	12	14	34	0.454
Total	15	30	25	70	
PSA-DT cutoff 45 days	**Gleason Score**			**Total**	**p**
	<7	7	>7		
PSA-DT ≤ 45 days	3	11	6	20	
PSA-DT >45 days	12	19	19	50	0.414
Total	15	30	25	70	

Table 3. PSA-DT according to clinical stage.

PSA-DT cutoff 75 days	Clinical Stage		Total	p
	≤T2	>T2		
PSA-DT ≤75 days	15	21	36	
PSA-DT >75days	20	14	34	0.116
Total	35	35	70	
PSA-DT cutoff 45 days	**Clinical Stage**		**Total**	**p**
	≤T2	>T2		
PSA-DT ≤45 days	7	13	20	
PSA-DT >45days	28	22	50	0.093
Total	35	35	70	

Table 4. PSA response rates to docetaxel chemotherapy.

PSA-R	≤50%	>50%
1.year	0.826 ± 0.091	0.72 ± 0.060
2.year	0.161 ± 0.102	0.581 ± 0.100
5.year	0.080 ± 0.076	0.090 ± 0.082
Median	21.37 ± 3.36	33.23 ± 3.67
95% GA	14 - 27	26 - 40
Log Rank	3.887	
p	0.049	

suggested to be a good predictor for survival rates [18]. Another study by Sengupta *et al.* showed that PSA-DT can be used as a prognostic factor for survival in patients receiving adjuvant hormonal therapy after radical prostatectomy [19].

The use of PSA-DT has been proposed as a value to classify the aggressiveness of prostate cancer [20]. Following this, many authors have demonstrated PSADT as a predictor of biochemical recurrence [14] [21]-[24].

To our own experience, some of the patients had a rising PSA after first dose of docetaxel. This does not mean a resistance to therapy or a clinical relapse or drug resistance in all cases. Still it makes the calculation of PSA-DT complicated. In addition, the PSA-DT may change for the same individual, at the different stages of the cancer [25] [26].

The previous studies generally focused on the correlation of PSADT for localized disease or biochemical relapse after curative treatments, but only a few studies have looked at PSA-DT for advanced disease.

Oudard and colleagues suggested that the PSA-DT over 45 days might be a valuable prognostic factor for survival for CRPC patients receiving docetaxel or mitoxantrone therapy [15]. Loberg *et al.* showed a significant

decrease in the PSADT between the hormone naive prostate cancer state versus the HRPC state in both the groups of 249 patients reviewed in their study [27].

PSA-DT was suggested to be used as a predictor for biochemical recurrence, and a possible sign for systemic disease [14] [20] [28].

In 2008 a meta-analysis for all PSA kinetics was published. This article showed that 54% of all the studies suggested that PSA kinetics were useful for prostate cancer prognosis regardless of disease stage [29]. After this review, in 2014, Vickers and colleagues presented their commentary about PSA kinetics for making decisions about biopsy and initial treatment. They presented that recent studies, including analyses of cohorts from all the major randomized trials of localized prostate cancer, have failed to find any evidence that PSA kinetics are of benefit in this setting [30].

In 2015, Murray *et al.* presented their study about PSA kinetics and bone marrow micrometastasis to define local or systemic relapse in men with biochemical failure after radical prostatectomy for prostate cancer. The authors suggested that PSA doubling time of <6 months or a total serum PSA of >2.5 ng/ml at the time of biochemical failure, the detection of bone marrow micrometastasis was significantly higher [31]. A recently published study from Chiaravalloti *et al.* showed that the use of PSA kinetics are helpful for selecting patients for PET/CT after radical prostatectomy [32]. Thomsen *et al.* presented their data on PSA kinetics for patients with localized prostate cancer. According to this the 13-year risk of mortality was associated with PSA-DT (≤3 years: 62.0% versus > 3 years: 16.3%, $P < 0.0001$) [33].

In 2016 Uchio and colleagues suggested that a PSA-DT ≤ 2 is useful to predict survival rates after radiation therapy, but on the other hand they couldn't find any significant predictive value for the patients who were treated by surgery first [34].

As a result, the main aim of the study was to evaluate if PSA doubling time was one of the prognostic factors for hormone refractory metastatic prostate cancer patients under docetaxel therapy. We found out no statistically significant proof for this hypothesis. In addition, we found that PSA response rate to chemotherapy is a very useful and valuable prognostic factor for this group of patients. If the patient had a >50% PSA response to docetaxel therapy, regardless of the timing of the response, the median survival rates were significantly higher. We need more studies to find better prognostic factors for survival in patients receiving docetaxel chemotherapy for prostate cancer.

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