



## Analyze of Risk Factors Affecting the Outcomes of Docetaxel-prednisone Combination in the Treatment of Metastatic Castration-resistant Prostate Cancer

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### Authors' contributions

This work was carried out in collaboration between all authors. Author BA designed the study, wrote the protocol and wrote the first draft of the manuscript. Authors MFA, OO and AIH managed the literature searches. Authors AO, CTG, BC and MA designed the figures, managed literature searches and contributed to the correction of the draft. All authors read and approved the final manuscript.

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### ABSTRACT

**Objective:** To analyze potential factors affecting the outcomes of docetaxel and prednisone (DP) combination therapy in patients with castration resistant prostate cancer (CRPC).

**Methods:** A total of 272 patients were treated with DP chemotherapy for CRPC between April 2006 and January 2014. Patients received docetaxel (75 mg/m<sup>2</sup>) administered as  $\geq$ 1-h intravenous infusion on day 1, every 3 weeks plus oral prednisone 5 mg twice daily starting on day 1 and continuing throughout the treatment. Patients were evaluated for prostate specific antigen (PSA) response, toxicity and factors affecting the treatment outcomes.

**Results:** 132 (48.6%) patients achieved a PSA response (47 complete and 85 partial response). There were no differences between PSA responders and PSA non-responders in terms of age, gleason score, initial PSA value and Eastern Cooperative Oncology Group (ECOG) performance status. Alkaline phosphatase (ALP) level of non-responders was significantly higher compared to

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PSA responders ( $p= 0.042$ ), total serum protein levels ( $p=0.035$ ) and albumin ( $p=0.012$ ) were significantly lower in non-responder group. Median survival rate of PSA responders was significantly higher compared to PSA non-responders (19 months vs 14 months,  $p= 0.000$ ). The most common grade 3-4 toxicity of chemotherapy was neutropenia which was observed in 95 (34.7%) patients. **Conclusions:** Serum ALP, total protein and albumin levels can be used to predict treatment outcomes following docetaxel and prednisone combination therapy in patients with CRPC.

**Keywords:** Docetaxel; prostate specific antigen; castration resistant prostate cancer; neutropenia.

## 1. INTRODUCTION

Androgen deprivation therapy in patients with metastatic prostate cancer (PC) provides symptomatic relief by producing a rapid improvement in bone pain and soft tissue metastasis, with initial response rates of about 80% and significant decrease in prostate specific antigen (PSA) [1]. Although most patients with advanced metastatic prostate cancer respond well to this treatment, the median duration of effective management in metastatic prostate cancer patients is between 18 and 24 months [2]. Castration resistant prostate cancer (CRPC) is defined as a rising PSA with castrate levels of serum testosterone and symptomatic progression plus radiologic evidence of progressive disease [3]. If hormonal manipulations fail, various modalities including chemotherapeutic regimens, vaccines (sipuleucel-T; an autologous cellular immunotherapy agent), second-line hormonotherapy with new drugs (Abiraterone, Enzalutamide), palliative radiotherapy or radium-223 (the only bone-specific drug that is associated with a survival benefit) for bone metastases, drugs targeting vascular endothelial growth factors (sunitinib and bevacizumab) can be used to control disease progression [4,5]. Docetaxel plus prednisone (DP) therapy has been established as a standard therapy for CRPC. Although new hormonal therapies are very effective in the treatment of CRPC, DP therapy is still considered as the first-line treatment due to high costs of new treatment modalities and financial limitations in social insurance systems.

Previous studies, which reported the efficacy of the mitoxantrone and corticosteroid (MC) combination therapy showed that MC could relieve metastasis related pain and decrease PSA values, but MC combination therapy provided no survival benefit in long-term follow-up [6,7]. Since 2004, treatment of CRPC has considerably evolved after TAX 327 and SWOG 99-16 studies [1,8,9]. According to the results of

these large randomized trials, the overall survival time, disease progression, pain control, quality of life and PSA response significantly improved with docetaxel treatment when compared with previous chemotherapy protocols [8,9]. However, many patients experienced considerable toxicities during docetaxel chemotherapy [10].

Docetaxel chemotherapy can lead to serious side effects in patients over 70 years of age and should be administered carefully. Currently, the identification of readily available prognostic factors is an essential step in optimizing the management of patients who are treated with docetaxel [10].

In this study, we aimed to analyze factors, which can potentially affect the outcomes of DP in the treatment of patients with CRPC.

## 2. MATERIALS AND METHODS

We retrospectively analyze 272 patients who were treated with DP chemotherapy for CRPC between April 2006 and January 2014. All patients had histologically confirmed adenocarcinoma of the prostate and disease progression was identified during androgen deprivation therapy. Anti-androgen therapy was discontinued 4-6 weeks before the administration of chemotherapy to allow the withdrawal of the anti-androgen therapy's effect. Testosterone levels were measured to confirm the castrated levels ( $<50$  ng/dl). Disease progression was defined with presence of one or more of the following criteria; at least two consecutive increases in PSA from the reference level measured prior to the initiation of the study regardless of any prior hormonal therapy and progression of measurable visceral and/or soft tissue lesions or appearance of new lesions. Patients received docetaxel administered 75 mg/m<sup>2</sup> of docetaxel as  $\geq 1$ -h intravenous infusion on day 1, and same dose repeated every 3 weeks. These patients also received 5 mg of oral prednisone twice daily, starting on day 1 and continued throughout the treatment. 8 mg of

Ondansetron was administered orally at the beginning of each treatment cycle to prevent emesis. All patients had an Eastern Cooperative Oncology Group (ECOG) performance status of  $\leq 2$  and hematological (leukocytes  $\geq 3000/\text{mm}^3$ ; hemoglobin  $\geq 10$  g/dl; and platelets  $> 10^5/\text{mm}^3$ ), renal (serum creatinine  $< 2.0$  mg/dl), and hepatic function tests (serum bilirubin  $< 2.0$  mg/dl) were all within normal limits. Patients who had previous chemotherapy, congestive heart failure, recent myocardial infarction or any other previous malignant disease except basal cell carcinoma of the skin were excluded from the study. All patients signed the informed consent form before chemotherapy. Before each cycle of chemotherapy, laboratory tests were conducted to determine the presence of any hematological, hepatic and renal toxicity. In case of severe toxicity, the treatment was delayed until the laboratory test values returned to normal. To evaluate the severity of toxicity, criteria of World Health Organization (WHO) were used.

All patients were evaluated for PSA response, toxicity and factors affecting treatment outcomes. The reference PSA level to evaluate PSA responses was measured within 2 weeks prior to DP therapy. Serum PSA level which was measured after the therapy was confirmed with measurement of a second PSA level 3 weeks later. We defined response categories as complete or partial response. Complete response (CR) was defined as a serum PSA level  $< 4.0$  ng/ml and partial response (PR) as at least 50% reduction in serum PSA levels. PSA progression during DP therapy was defined as at least 25% increase in serum PSA levels or an increase from a value within the normal limits to an abnormal value [11].

In order to compare the clinical and pathological differences of treatment outcomes according to PSA responses, Mann-Whitney U test, Chi-square and Fishers exact tests were used. Statistically significant parameters in the univariate analysis were included in the multivariate model. A survival analysis was performed using Kaplan-Meier method. The log-rank test was used to compare the groups. A p value  $< 0.05$  was considered to indicate statistical significance. Statistical analyses were performed using SPSS software version 17.0, Chicago IL.

### 3. RESULTS

Demographic and disease characteristics for all patients were summarized in Table 1. Mean age

of the patients was  $70.1 \pm 7.4$  years (53-89). All patients received maximal androgen blockage (MAB) therapy with luteinizing hormone releasing hormone (LH-RH) agonist or bilateral orchiectomy plus antiandrogen. 26(9.7%) patients underwent radical retropubic prostatectomy and 49 (18.0%) patients received radiotherapy before hormonal therapy. The number of patients with Gleason scores 7, 8 and 9 were 79(29.1%), 60(22.2%) and 133(48.7%), respectively. According to ECOG performance status, 226(83.3%) patients had a performance status of 0, 34(12.5%) patients had a performance status of 1 and 12(4.2%) patients had a performance status of 2. All patients with metastatic disease had bone metastasis. Additionally, 3 patients had lymph node metastasis, 1 patient had liver and 1 had lung metastasis. Initial median PSA value was 41.60ng/ml (range 3.40-843). Mean hemoglobin value was  $10.6 \pm 0.2$  gr/dl; mean ALP level was  $371 \pm 107$  IU/L; and mean lactate dehydrogenase (LDH) was  $231 \pm 76$  IU.

The median follow-up period was 27.1 months (3-52). Patients received 8.8 cycles of DP treatment in average. Complete response was achieved in 47 patients and partial response was achieved in 85 patients. There were no differences between PSA responders and non-responders in terms of age, Gleason score, initial PSA value and ECOG performance status. On the other hand, serum ALP level of non-responders was significantly higher when compared to PSA responders (447 IU/L vs. 292 IU/L) ( $p = 0.042$ ). Total protein ( $p = 0.035$ ) and albumin levels ( $p = 0.012$ ) were significantly lower in the non-responder group (Table 2).

Initial PSA (18.5ng/ml vs. 51.8ng/ml,  $p = 0.046$ ) and ALP (101.7 IU/L vs 417 IU/ L,  $p = 0.038$ ) levels were significantly lower in patients with complete response when compared to the patients with partial response (Table 3). The duration of PSA response was 7.4(5-10) and 5.2(2-7) months in patients with complete and partial response, respectively ( $p = 0.009$ ). 151 of our patients experienced serious pain before the treatment and analgesic drug intake was reduced in 52 (34%) of those patients. The median survival rate of the PSA responders was significantly higher than the PSA non-responders (19 months vs 14 months,  $p = 0.000$ ) (Fig. 1).

Although univariate analysis revealed that there were statistically significant differences in levels of ALP, total protein, and albumin between PSA

responders and PSA non-responders (Table 2), multivariate analysis revealed serum albumin level as the single significant parameter when two groups are compared. (OR=10.8; 95% CI (1.5-78.2);  $p < 0.001$ ).

**Table 1. Patients' characteristics**

Characteristics	Number of patients $\pm$ SD
Age; mean (years)	70.1 $\pm$ 7.4
<b>Baseline PSA;</b>	
mean (ng/ml)	107.9 $\pm$ 176.7
median (ng/ml)	41.6 (3.40 – 843)
Hb; mean (gr/dl)	10.6 $\pm$ 0.2
ALP; mean (IU/l)	371 $\pm$ 107
LDH; mean (IU/l)	231 $\pm$ 76
Total protein; mean (g/dl)	6.6 $\pm$ 0.09
Albumin; mean (g/dl)	3.9 $\pm$ 0.06
<b>Gleason score</b>	
7	79 (29.1%)
8	60 (22.2%)
9	133 (48.7%)
Pain	151(55.5%)
<b>ECOG score</b>	
0	226 (83.3%)
1	34 (12.5%)
2	12 (4.2%)
<b>Prior treatment</b>	
Radical prostatectomy	26 (9.7%)
Radiotherapy	49 (18.0%)
Hormonotherapy	197 (72.3%)
<b>Metastasis</b>	
Bone	266 (98.0%)
Lymph node	3 (1.1%)
Visceral	2 (0.7%)
Number of cycles; mean	8.8 $\pm$ 4.7

The most common toxicity was bone marrow suppression and the most common grade 3 and 4 toxicity of chemotherapy was neutropenia, which was seen in 95 of 272 (34.7%) patients. 99 (33.4%) had grade 3-4 leukopenia, 76 (27.8%) had grade 1-2 neutropenia, 37(13.8%) had grade 1-2 leukopenia and 171 (62.5%) had grade 1-2 thrombocytopenia. Granulocyte-colony stimulating factor was administered to 106(38.8%) patients. The most frequent non-hematological side effects were general fatigue (53.6%) and diarrhea (12.1%). Maculopapular rash and oral candidiasis which were observed in two different patients were treated with topical agents.

#### 4. DISCUSSION

With the development of new chemotherapy protocols, many studies demonstrated

improvement in survival of patients with CRPC. In 2004, two randomized trials (TAX 327 study and the SWOG trial) showed a significant survival advantage in the treatment of these patients with chemotherapy and docetaxel treatment has been established as standard chemotherapy for CRPC [6,7]. The regimen of 3 weekly docetaxel (75 mg/m<sup>2</sup>) plus low dose prednisone has been widely considered to be the recommended treatment of choice for symptomatic, metastatic CRPC [1]. Several alternative agents including hormone derivatives and chemotherapeutic drugs are continued to be investigated. In patients with relapse following docetaxel chemotherapy, cabazitaxel, abiraterone and enzalutamide are regarded as first-choice options for second-line treatment in CRPC. Abiraterone inhibits cytochrome P17 enzyme which is expressed in testicular, adrenal, and prostatic tumor tissues and is required for androgen biosynthesis. Enzalutamide has been shown to competitively inhibit androgen binding to androgen receptors and inhibit androgen receptor nuclear translocation and interaction with DNA [12,13]. Outcomes of further clinical investigations will possibly change the guidelines in the close future.

There are certain prognostic factors affecting disease progression and survival in docetaxel chemotherapy but no consensus exists about these prognostic factors [14]. Qu et al. [10] investigated possible prognostic factors for overall survival in patients with metastatic CRPC who have treated with docetaxel-based chemotherapy. The authors stated the significance of several independent prognostic factors including PSA doubling time, baseline hemoglobin (Hb) concentration, cycles of chemotherapy and time to castration resistance. An increase in ALP level was previously thought to be a substitute for bone scans progression as prognostic factor [14]. The significance of ALP for evaluating bone metastasis was also reported in previous studies [15,16]. Armstrong et al. [17] investigated pre-treatment factors predicting PSA decline and overall survival in men treated with docetaxel chemotherapy by subgroup analysis of TAX327. They found four independent risk factors for PSA decline and overall survival. These factors were pain, visceral metastases, anemia and bone scan progression. Saad et al. investigated PSA kinetics and outcomes in treated with or without zoledronic acid [18]. The authors concluded that PSA is an important prognostic tool for survival in patients with CRPC who had bone metastasis, and PSA is also

prognostic for bone disease progression and skeletal associated events. De Bono et al. mentioned the effect of circulating tumor cells on survival benefit in the treatment of CRPC [19]. Bournakis et al. emphasized time to castration resistance as an independent factor of castration resistant prostate cancer survival [20]. Our study

showed that patients with high baseline ALP concentration, low total protein and albumin levels had lower response to docetaxel chemotherapy. Although there are many risk factors affecting treatment results, albumin level was found to be a significant parameter in multivariate analysis.

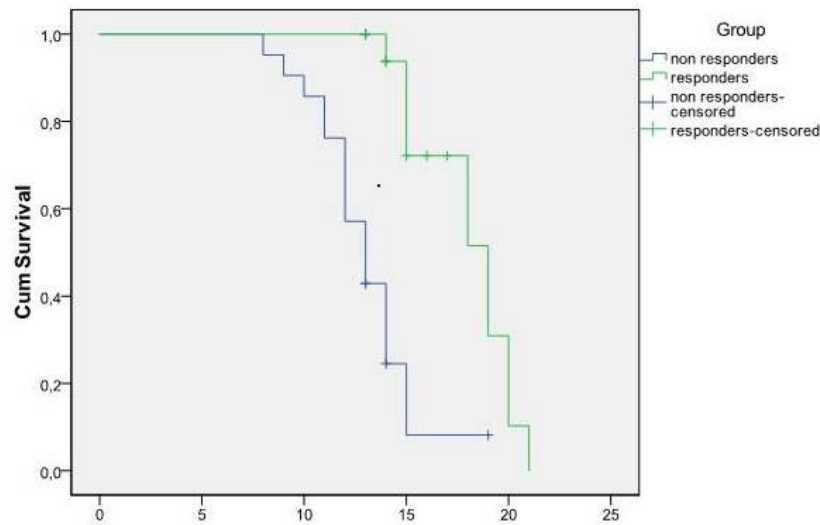


Fig. 1. The median survival rate between responders and non-responders

Table 2. Comparison of clinical features of PSA responders and non-responders

Characteristics	PSA responder n= 132	PSA non-responder n= 140	p value
Age; mean (years)	69.6	70.7	0.520
Baseline PSA; mean (ng/ml)	52.1	161.1	0.108
median (ng/ml)	30.9	120	
Hb; mean (gr/dl)	10.8	10.5	0.566
ALP; mean (IU/l)	292	447	<b>0.042</b>
LDH; mean (IU/l)	238	224	0.215
Total protein; mean (g/dl)	6.92	6.45	<b>0.035</b>
Albumin; mean (g/dl)	4.13	3.82	<b>0.012</b>
<b>Gleason score</b>			
7	41	38	0.286
8	18	42	
9	73	60	
Reduction in analgesic requirements	30	22	0.477
<b>ECOG score</b>			
0	115	111	0.246
1	12	22	
2	5	7	
<b>Prior treatment</b>			
Radical prostatectomy	14	12	0.677
Radiotherapy	21	28	
Hormonotherapy	97	100	
Number of cycles; mean	9.1±3	8.7±6	0.158

**Table 3. Comparison of patients with complete and partial PSA response**

<b>Characteristics</b>	<b>Complete PSA response n= 47</b>	<b>Partial PSA response n= 85</b>	<b>p value</b>
Age; mean (years)	68.3	71.9	0.631
Baseline PSA; mean (ng/ml)	31.6	63.2	<b>0.046</b>
median (ng/ml)	18.5	51.8	
Hb; mean (gr/dl)	11.6	10.9	0.311
ALP; mean (IU/l)	101.7	417	<b>0.038</b>
LDH; mean (IU/l)	201	266	0.326
Total protein; mean (g/dl)	7.0	6.7	0.415
Albumin; mean (g/dl)	4.2	4.1	0.744
<b>Gleason score</b>			
7	18	23	0.451
8	4	14	
9	25	48	
<b>ECOG score</b>			
0	41	74	0.575
1	4	8	
2	2	3	
Number of cycles; mean	9.7	8.3	0.512
Duration of PSA response (months);mean	7.4	5.2	<b>0.009</b>

In our study, PSA response rate was 48.6% and median overall survival was 19.1 months. Our results are comparable with those from TAX 327 study with a PSA response of 45% and a median overall survival of 19.2 months [8,21]. In another study, median survival was found to be 15.9 months with a PSA response time of 6.8 months in 88 men with CRPC [22]. In a phase II study of docetaxel re-treatment in docetaxel- pretreated CRPC patients, the authors showed that docetaxel re-treatment preserves antitumor activity and is well tolerated in a selected population of pretreated patients with CRPC [21]. In a recent randomized phase II study comparing docetaxel and epirubicin (D/EPI) with docetaxel and prednisone(D/P) in advanced castrate-resistant prostate cancer, the median survival was 27.3 months in the D/EPI arm and 19.8 months in the D/P arm [23]. All studies including the current study found survival advantage with good tolerance, which provides docetaxel-based chemotherapies as the standard of care for men with metastatic CRPC.

Bone metastasis can be seen in different stages of metastatic disease and have an important role in the treatment design. ALP is an important marker for evaluating bone metastasis. Kawahara et al. used ALP as a surrogate marker of bone scan and found a significant association with overall survival and a higher ALP level [14]. Sonpavde et al. [16] mentioned total serum ALP

as a relatively nonspecific marker which can increase in case of liver or bone metastasis. However, patients with bone metastasis and an elevated baseline ALP were likely to have bone as the dominant source of ALP. In the present study, patients with complete response had lower ALP levels than partial responders ( $p= 0.038$ ). It is doubtless that none of the risk factors can be a unique reason for the evaluation of treatment response due to variable etiologies in the natural formation of prostate cancer. However, high baseline ALP levels may predict a possible increase of mortality in metastatic CRPC patients. Our study revealed that total protein and albumin levels are also associated with the response to docetaxel chemotherapy.

Toxic side effects of a chemotherapy regimen are crucial to completely terminate the therapy. Hematological toxicity, particularly neutropenia and neutropenic sepsis, is always a challenge with chemotherapy regimens utilizing docetaxel. Several previous studies showed acceptable adverse events with docetaxel [1,23-28]. The most common side effects were fatigue, diarrhea and skin rashes. In our study, grade 3 and 4 neutropenia was recorded in 95 patients (34.7%) with febrile neutropenia in 22 patients (8.3%). 38.8% of the patients were treated with granulocyte colony-stimulating factor. Grade 1 or 2 thrombocytopenia was also identified in more than half of our patients.

## 5. CONCLUSION

DP combination therapy is a suitable and effective regimen with acceptable tolerance in the treatment of men with CRPC. Serum ALP, total protein and albumin levels can be used to predict chemotherapy outcomes following DP chemotherapy in patients with CRPC.

## ETHICAL APPROVAL

All procedures were in accordance with the standards of the Committee for Human Experimentation with the 1964 Helsinki Declaration and the Committee on Publication Ethics guidelines. The study was conducted with the approval of the local ethical committee of Taksim Training and Research Hospital (Istanbul, Turkey). Informed written consent was obtained from all patients or their relatives.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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