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Effectiveness and safety of cabazitaxel chemotherapy for metastatic castration-resistant prostatic carcinoma on Turkish patients (The Anatolian Society of Medical Oncology)

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Abstract. – OBJECTIVE: Prostate cancer is among the most common cancers in males. Prostate cancer is androgen dependent in the beginning, but as time progresses, it becomes refractory to androgen deprivation treatment. At this stage, docetaxel has been used as standard treatment for years. Cabazitaxel has become the first chemotherapeutic agent which has been shown to increase survival for patients with metastatic Castrate Resistant Prostate Cancer (mCRPC) that progresses after docetaxel. Phase 3 TROPIC study demonstrated that cabazitaxel prolongs survival.

PATIENTS AND METHODS: In this study, we evaluated a total of 103 patients who took cabazitaxel chemotherapy for mCRPC diagnosis in 21 centers of Turkey, retrospectively. This study included patients who progressed despite docetaxel treatments, had ECOG performance score between 0-2, and used cabazitaxel treatment. Patients received cabazitaxel 25 mg/m^2 at every 3 weeks, and prednisolone 5 mg twice a day.

RESULTS: Median number of cabazitaxel cures was 5.03 (range: 1-17). Cabazitaxel response evaluation detected that 34% of the patients had a partial response, 22.3% had stable disease and 32% had a progressive disease. Grade 3-4 hematological toxicities were neutropenia (28.2%), neutropenic fever (14.5%), anemia (6.7%), and thrombocytopenia (3.8%). In our study, median progression-free survival (PFS) was 7.7 months and overall survival (OS) was 10.6 months.

CONCLUSIONS: This study reflects toxicity profile of Turkish patients as a Caucasian race. We suggest that cabazitaxel is a safe and effective treatment option for mCRPC patients who progress after docetaxel. Moreover, ethnicity may play important roles both in treatment response and in toxicity profile.

Key Words:
Prostate cancer, Cabazitaxel, Chemotherapy, Toxicities.

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Introduction

Prostate cancer is the most common cancer of males in developed countries and it is the second most common cause of cancer-related deaths. Screening programs using prostate-specific antigen (PSA) increased diagnosis of prostate cancer and decreased its mortality rate[1].

Prostate cancer is initially androgen-dependent. Since orchiectomy was detected to provide regression in prostate cancer approximately 70 years ago, antiandrogen treatment (medical or surgical castration) forms basis of metastatic prostate cancer treatment[2].

Although most patients respond to hormonal treatment, serological or radiological progression is seen at mean 12-24 months later[3].

Until 2004, there was no alternative treatment that prolonged overall survival (OS) in metastatic Castrate Resistant Prostate Cancer (mCRPC) treatment. Two randomized trials published in 2004 (TAX 327 and SWOG 99-16) demonstrated that docetaxel increased OS and improved quality of life in mCRPC treatment[4,5].

The first chemotherapeutic agent detected to prolong survival in mCRPC patients who progress after docetaxel was cabazitaxel. In phase 3 TROPIC study median survival was 15.1 months in cabazitaxel/prednisone arm and 12.7 months in mitoxantrone/prednisone arm[6].

Taxanes are a novel chemotherapeutic drugs class which have been used in last 20 years for the treatment of several solid tumors[7,8]. But their high affinity to multidrug resistance protein (MDR) is their most important potential limitation. Both structural (genetic, constitutive), and acquired resistance may develop against taxanes[9,10]. As a new generation taxane, cabazitaxel shows low affinity to ATP-dependent drug efflux pump, P-glycoprotein 1 (P-gp). In addition, it has higher blood brain barrier penetration than docetaxel and paclitaxel[11].

In this study, we retrospectively evaluated treatment response and toxicity data of 103 patients who were detected to have mCRPC and treated with cabazitaxel in 21 centers in Turkey.

Patients and Methods

A total of 103 patients who took cabazitaxel chemotherapy for mCRPC in 21 centers in Turkey were retrospectively evaluated. Patients data were obtained from clinical and histopathological diagnostic records. All of the patients had prostatic adenocarcinoma diagnosis histopathologically. They were refractory to antiandrogen treatment and their mean testosterone concentration was at castration level. Patients who previously took docetaxel treatment, had ECOG performance score of 0-2 and who were taking cabazitaxel treatment were included in this study. The patients received cabazitaxel 25 mg/m^2 at every third week and prednisolone 5 mg bid. When dose reduction was required due to toxicity, 20 mg/m^2 dosage was applied.

Statistical Analysis

All data were analyzed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA) software. The clinicopathological factors of patients were compared using the chi-square and Fisher's exact tests. Actuarial survival was determined by Kaplan-Meier analysis. Tumor response rates were evaluated as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) according to the RECIST criteria. Progression-free survival (PFS) was defined as no progression after cabazitaxel use. Overall survival (OS) was defined as survival after administration of cabazitaxel and death. The relationships between patient, tumor, and treatment characteristics with outcome were tested by univariate analysis using a log-rank test. Multivariate analysis was performed using the Cox proportional hazards model, and the only variables that were deemed statistically significant were included in the final Cox model. Multivariate *p-values* were used to characterize the independence of these factors. The 95% confidence interval (CI) was used to quantify the relationship between survival time and each independent factor. All *p-values* were two-sided in the tests and *p*-values less than 0.05 were considered to be statistically significant.

Results

Data of 103 patients who got cabazitaxel treatment between April 2012 and December 2014 in 21 centers in Turkey were retrospectively evaluated. The mean age of the patients was 66.19 (37-83) years. The median Gleason Score was 7.98 (6-10). In 89.3% of the patients there was bone metastasis and in 38.8% there was visceral metastasis. Surgical castration (orchiectomy) was performed to 16.5% of the patients. Eighty-one

patients (78.6%) received palliative radiotherapy (RT) and 59 patients (57.2%) received multiple palliative RT. Total docetaxel dosage taken by the patients was median 562 (270-690) mg/m^2. Before initiation of cabazitaxel ECOG status of 76.7% of the patients was 0-1, and 23.3% was 2 (Table I).

The median number of cabazitaxel cures was 5.03 (range: 1-17). Cabazitaxel response was followed by radiological and serological methods in 20% of patients and by serological and clinical methods (worsening of symptoms or cancer pain) in 80% of the patients. Cabazitaxel response evaluation revealed partial response in 34%, stable disease in 22.3%, and progressive disease in 32% of the patients. Prior treatment, the median PSA level was 228.1 (36-1123) ng/ml and, after treatment, the median PSA level was 103.9 (3-450) ng/ml.

Evaluation of hematological toxicity (Table II) revealed grade 3-4 toxicities like neutropenia in 28.2%, neutropenic fever in 14.5%, anemia in 6.7% and thrombocytopenia in 3.8% of the patients.

Other grade 3-4 toxicities were nausea (5.8%), vomiting (2.9%), diarrhea (7.7%), anorexia (4.8%), and fatigue (7.7%). Toxic deaths were seen in 3 patients (2.3%). The dose was reduced in 24.3% of the patients due to toxicity and delayed in 26.2%. The primary GCSF prophylaxis was given in 70.9% of the patients.

In our study, median PFS was 7.7 months (95% CI: 5.41-10.16) (Figure 1), and median OS was 10.6 months (95% CI: 8.51-10.70) (Figure 2).

No significant relation was found between age, objective response, Gleason score, presence of comorbidity, ECOG performance status, delay in treatment, dose reduction, and presence of solid organ metastasis and PFS or OS. Although no relation was found between number of cabazitaxel cures (number of cures < 6 or > 6) and PFS, OS significantly increased in patients taking 6 or more cures (*p*-values: 0.002) (Figure 3).

Table I. Patient and disease characteristics (n 103).

Characteristic	No. Patient (%)
Age	
Median (year)	66.19
≥ 70	34 (35.02)
ECOG status	
0-1	79 (76.7)
2	24 (23.3)
Gleason skoru (median)	7.98
Cumulative docetaxel doses (mg/m^2)	562.5
Sites of metastases	
Bone	92 (89.3)
Lung	11 (10.6)
Liver	8 (7.7)
Any other viscera	19 (18.4)
Androgen deprivation	
Medical castration	86 (83.5)
Orchiectomy	17 (16.5)

Discussion

In recent years[12], randomized studies demonstrated that 5 new drugs (sipuleucel-T, cabazitaxel, abiraterone acetate, alpharadin, and enzalutamide) have shown to increase survival in mCRPC treatment. After TROPIC study cabazitaxel was the first agent that has been shown to increase

Table II. Most common treatment emergent grade 3-4 toxicity.

	Toxicity*	All grades n (%)	Grade ≥ 3 n (%)
Hematological	Neutropenia	61 (59.2)	29 (28.2)
	Febrile neutropenia	15 (14.5)	15 (14.5)
	Anemia	59 (57.2)	7 (6.7)
	Thrombocytopenia	31 (30)	4 (3.8)
Non-hematological	Diarrhea	25 (24.2)	8 (7.7)
	Nausea	55 (53.3)	6 (5.8)
	Vomiting	38 (36.8)	3 (2.9)
	Anorexia	42 (40.7)	5 (4.8)
	Fatigue	36 (34.9)	8 (7.7)
	Peripheral neuropathy	15 (14.5)	–
	Toxic death	–	3 (2.3)

*Toxic effects were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (v. 4.0)

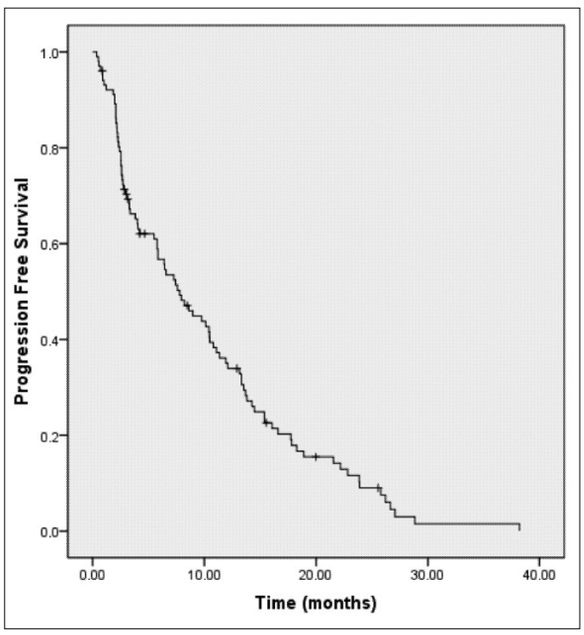

Figure 1. Progression free survival.

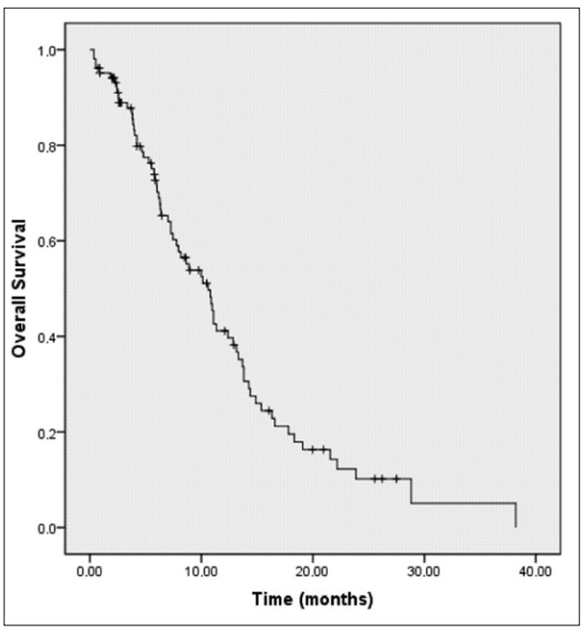

Figure 2. Overall survival.

survival after Docetaxel and it decreases the risk of death 30% compared with mitoxantrone[6].

This study retrospectively evaluated data of 103 patients in 21 centers in Turkey who were treated with cabazitaxel. In this study, median PFS was 7.7 months and median OS was 10.6 months. PFS value was longer than both 2.8 months reported in TROPIC Study[6] and 3.9

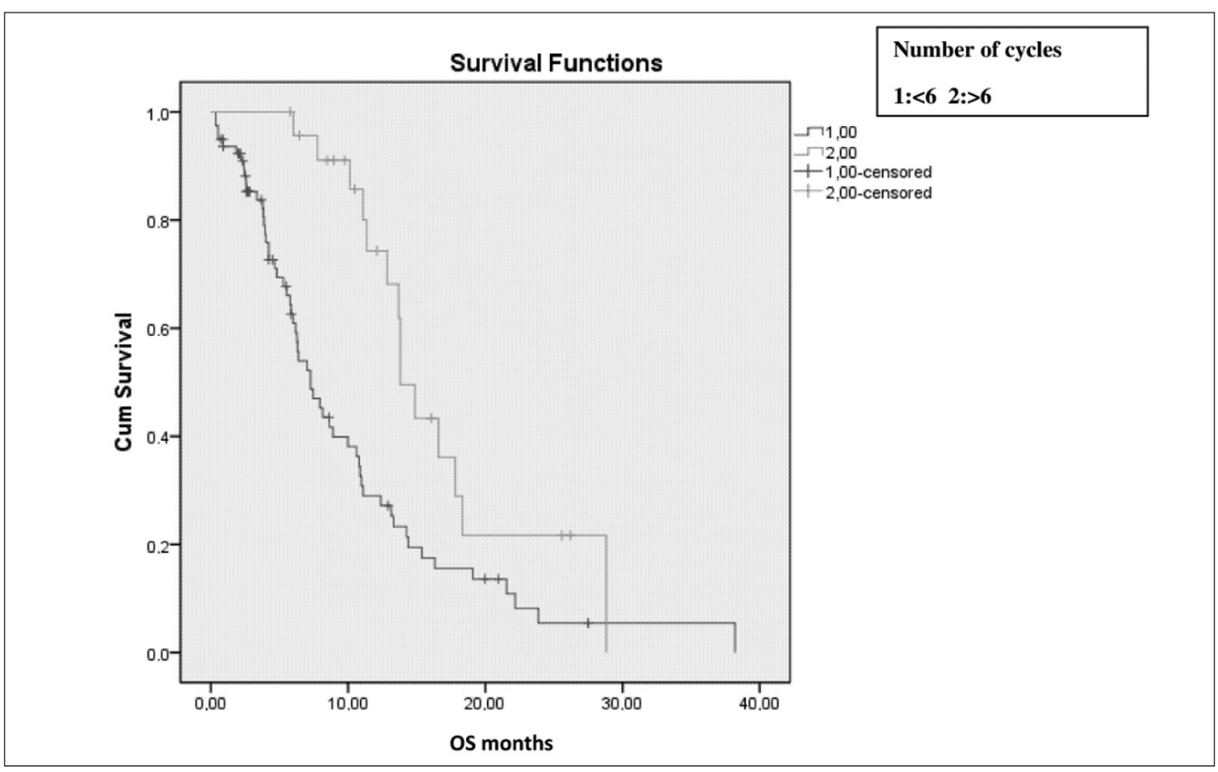

Figure 3. Significantly longer overall survival in patients taking more than 6 cures.

months reported in German Compassionate-Use Programme (CUP) study[13]. But PFS was reported to be 8.5 months in Korean Compassionate-Use Programme[14]. OS value of 10.6 months was shorter than 15.1 months reported in TROPIC study. We think that ECOG performance status of 2 in 23% of our patients led to lower than expected median OS value. Taxanes are metabolized by cytochrome P450 enzyme system in the liver. Therefore, ethnicity may play a role in the effectiveness and toxicity of cabazitaxel[14]. Evaluation of grade 3-4 hematological toxicities in our study revealed that neutropenia occurred in 28.2% and neutropenic fever occurred in 14.5% of the patients. Primary prophylactic GCSF was used in 70.9% of the patients. Thus, lower neutropenia rate than TROPIC study is an expected finding in our study. But the rate of neutropenic fever was higher than TROPIC study[6]. German CUP Study[13] reported very low rate of neutropenic fever (1.8%) but it was higher (31%) in Korean CUP study[14]. Anemia (6.7%) and thrombocytopenia (3.8%) were seen at expected rates. Diarrhea (7.7%) and nausea (5.8%) were the highest grade 3-4 non-hematological toxicities which were seen at higher rates than TROPIC study. In our study, the dose reduction was needed in 24.3% and dose delaying in 26.2% due to toxicity. Dose reduction due to toxicity was reported in 12% in TROPIC study and in 52% in Korean CUP and this difference was attributed to ethnicity. Treatment-related mortality rate, which was reported to be 5% in TROPIC study, was detected to be 2.3% in our study.

This study is important as it reflects toxicity profile of Turkish (a Caucasian race) patients. Another important finding of our study is the detection of significantly longer OS in patients taking more than 6 cures. Our study offers valuable information, as Della Pepa et al[15] stressed in the real world Works, also.

Conclusions

We think that cabazitaxel is a safe and reliable treatment option in patients who shows progression after docetaxel treatment. Good toxicity management, particularly for hematological toxicities and proactive support measures such as prophylactic GCSF use, should not be discarded. Also, ethnicity may play an important role both in treatment response and in toxicity profile.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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