Comparing the Efficacy of Cabazitaxel in Second-Line and Third-Line Treatment of Metastatic Castration-Resistant Prostate Cancer: A Multi-Center Experience from Turkey

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ABSTRACT

Introduction: Prostate cancer is the most common type of cancer in men and is the second most common cause of cancer-related death in the United States. Objective of this study was to investigate the efficacy and toxicities of cabazitaxel in the second-line and third-line treatment of metastatic castration-resistant prostate cancer (MCRPC) with real-life data.

Material and Methods: Patients who progressed with docetaxel and received cabazitaxel in the second-line and third-line for mCRPC treatment were included in the study. Progression-free survival (PFS) was defined as the time from the onset of cabazitaxel to clinical, radiological or prostate specific antigen (PSA) progression. Median PFS and cabazitaxel-related toxicities were compared between the second-line and third-line.

Results: The median age of the 73 patients included in the study was 65 (53-80) years. All patients had bone metastasis and 17 (23.3%) patients had visceral metastasis. Cabazitaxel was applied as second-line treatment in 38 (52.0%) patients and as third-line treatment in 35 (47.9%) patients. Median 7(1-16) cycles of cabazitaxel were received. Median PFS was 7.9 months in the second-line treatment and 5.6 months in the third-line treatment (p:0.862). It was observed that 87.6% (n: 64) of the patients had any grade cabazitaxel-related side effects. There was no difference between the second-line and third-line cabazitaxel-related toxicities.

Conclusion: In conclusion, cabazitaxel was found to have similar efficacy in second and third-line treatment of mCRPC in our study. There was no difference between the two group in terms of toxicity.

Keywords: Cabazitaxel, Prostat Cancer, PSA, Castration Resistant

INTRODUCTION

Castration-resistant prostate cancer (CRPC) has been defined as a progressive disease despite androgen depletion therapy.[1,2]

While only docetaxel is known to be effective in the treatment of metastatik CRPC (mCRPC) until 2010, significant improvements in survival have been achieved in recent years with new therapies such as new generation androjen signalling inhibitors (abireterone, enzalutamide), immunotherapy (spilucel-t), radioactive agent (radium-223) and new generation taxane (cabazitaxel).[3-7]

Cabazitaxel is a new generation synthetic taxane derivative. The Phase III TROPIC study demonstrated its efficacy in the treatment of mCRPC after docetaxel. Cabazitaxel appears to be less toxic than docetaxel and it was approved by the FDA in 2010.

Cabazitaxel is the first agent that has shown a survival benefit in the treatment of mCRPC after docetaxel, but other agents have been shown to be effective in this step in the following years. However, there is no clear data on the sequential use of cabazitaxel, androgen signaling inhibitors, immunotherapy and radiopharmasotic agents in the treatment of mCRPC.[8] In addition, the efficacy and toxicity of cabazitaxel in the treatment of MCRPC after second-line are not well known.

In this study, we aimed to evaluate the efficacy and toxicities of cabazitaxel in the second-line and third-line treatment of mCRPC with real-life data.

MATERIAL AND METHODS

Study design and setting

This study was a retrospective cohort study. Patients who received cabazitaxel for the treatment of mCRPC between August 2012 and May 2019 were retrospectively evaluated. Four centers in Turkey participated in the study. We

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performed the study after the ethical approval was obtained from Health Sciences University, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Reseaarch Hospital Ethics Committee.

Patients

Male patients over 18 years of age who progressed with docetaxel, and received cabazitaxel in the second-line and third-line for mCRPC treatment were included in the study. Patients who received cabazitaxel in the later-lines were excluded from the study.

Variables and outcomes

The demographic and clinicopathological features of the patients were recorded by examining the patient files and electronic registry system. Diabetes mellitus, hypertension, cardiovascular diseasese, rheumatologic diseases and chronic obstructive pulmonary disease were accepted as comorbidity. The treatments that the patients received before and after cabazitaxel for the treatment of mCRPC, the dates of first and last cabazitaxel administration, side effects related to cabazitaxel, progression and mortality status, and time of progression or death were recorded.

The primary outcome of this study was to compare progression-free survival (PFS) which obtained with cabazitaxel in the second-line and third-line treatment of mCRPC.

STATISTICAL ANALYSIS

Data were analyzed using the IBM Statistical Package for Social Sciences (SPSS®) v.23.0 (IBM Inc.; Armonk, NY, USA).

PFS was defined as the time from the onset of cabazitaxel to progression or death according to the criteria of Prostate Cancer Clinical Trials Working Group 2.[9]

Kaplan-Meier method was used for PFS calculation. The median PFS according to treatment lines was compared with log-rank test. Univariate analysis was performed to evaluate the independent prognostic factors affecting PFS. Cox proportional hazard model was used for 95% hazard ratio safety range. Chi-Square and Fisher's exact tests were used to evaluate categorical variables. P <0.05 was considered significant.

RESULTS

The median age of the 73 patients included in the study was 65 (53-80) years. The Eastern Cooperative Oncology Group (ECOG) performance score of the majority of patients was 0 or 1 (n: 60, 82.2%). Twenty-nine (39.7%) patients had at least one comorbid disease. All patients had bone metastasis and 17 (23.3%) patients had visceral metastasis. Patient characteristics are shown in Table-1.

The majority of patients (n: 66, 90.4%) received docetaxel at the first line treatment of mCRPC. Cabazitaxel was applied as second-line treatment in 38 (52.0%) patients and as third-line treatment in 35 (47.9%) patients. Median 7 (1-16) cycles of cabazitaxel were received . Cabazitaxel was administered at a dose of 25 mg/m2 in 36 (50.6%) patients and 20 mg/m2 in 36(49.3%) patients once every three weeks.

The median PFS in the whole patient population was 7.0 months (95% confidence interval [CI], 5.2-8.8). Median PFS was 7.9 months in the second-line treatment and 5.6 months in the third-line treatment; this difference was not statistically significant (p:0.862, Figure 1).

Age, ECOG performance score, comorbidity, visceral involvement and cabazitaxel dosage were not associated with PFS. Gleason score had an effect on PFS (p: 0.004, Table 2).

Primary prophylaxis with granulocyte colony stimulating factor (G-CSF) was administered to 90.4% (n:66) of patients. When the side effects were examined, it was observed that 87.6% (n: 64) of the patients had any grade cabazitaxel-related side effects. Twenty-four (32.8%) patients had chemotherapy delay due to toxicity. Although primary G-CSF prophlaxis was applied to the majority of patients

	n: 73	%
Age Median (range) - yr	65 (53-80)	
ECOG performance status score		
0 or 1	60	82.2
2	13	17.8
Comorbidity		
Yes	29	39.7
No	44	60.3
Gleason score		
7	13	17.8
8	25	34.2
9	35	47.9
Site of metastasis		
Bone	44	60.4
Bone and lymph node	12	16.3
Bone and visceral	17	23.3
Firstline treatment		
Docetaxel	66	90.4
Enzalutamide	4	5.5
Abiraterone	3	4.1
Secondline treatment		
Cabazitaxel	38	52.0
Abiraterone	21	28.7
Docetaxel	7	9.5
Enzalutamide	7	9.5
Thirdline treatment		
Cabazitaxel	35	47.9
Abiraterone	28	38.3
Enzalutamide	7	9.5
None	3	4.1
Cabazitaxel sequence		
2nd line	38	52.0
3nd line	35	47.9
Cabazitaxel dosage		
20 mg/m^2	36	49.3
25 mg/m^2	37	50.6
Primary prophylaxis with G-CSF	66	90.4

Table-1: Patient characteristics

	n (%)	HR	95% CI	p-value
Age (yr)				
<65	34 (46.5%)	0.909	0.565-1.464	0.695
≥65	39 (53.4%)			
ECOG performance status score				
0 or 1	60 (82.2%)	0.911	0.495-1.677	0.764
2	13 (17.8%)			
Comorbidity				
Yes	29 (39.7%)	1.010	0.621-1.643	0.967
No	44 (60.3%)			
Gleason score				
7-8	38 (52.0%)	2.104	1.271-3.481	0.004
9	35 (47.9%)			
Cabazitaxel sequence				
2nd line	38 (52.0%)	1.042	0.648-1.677	0.864
3th line	35 (47.9%)			
Cabazitaxel dosage				
20 mg/m^2	36 (49.3%)	0.997	0.620-1.602	0.989
25 mg/m^2	37 (50.6%)			
Visceral metastasis				
No	56 (76.7%)	1.616	0.901-2.897	0.107
Yes	17 (23.3%)			

Table-2: Univariate analysis of progression free survival

	All patients n:73	2nd line n:38	3th line n:35	P value
Toxicity	64 (87.6)	35 (92.1%)	29 (82.8%)	p:0.23
Fatigue	42 (57.5%)	20 (57.8%)	22 (62.8%)	p:0.377
Diarrhea	26 (35.6%)	13 (34.2%)	13 (37.1%)	p:0.794
Nause or vomiting	15 (20.5%)	8 (21.0%)	7 (20.0%)	p:0.911
Febrile neutropenia	10 (13.6%)	6 (15.8%)	4 (11.8%)	p:0.738
Peripheral neuropathy	8 (10.9%)	4 (10.5%)	4 (11.4%)	p:0.597
Chemotherapy delay	24 (32.8%)	13 (34.2%)	11 (32.4%)	p:0.8
Dose reduction	12 (16.4%)	7 (18.4%)	5 (14.2%)	p:0.634
Discontinuation of treatment	4 (5.4%)	3 (7.8%)	1 (2.8%)	p:0.616
Chemotherapy related death	2 (2.7%)	2 (5.3%)	0	p:0.494

Table-3: Cabazitaxel related toxicity (any grade)

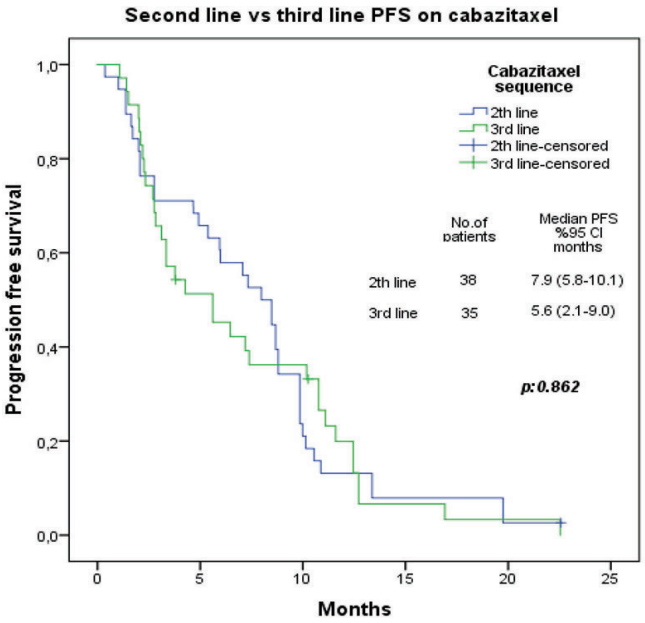

Figure-1: Second-line vs third-line PFS on cabazitaxel

(90.4%), febrile neutropenia (FN) was observed in 10 (13.6%) patients. One of these patients died due to sepsis. Another patient died of grade 4 thrombocytopenia and grade 3 diarrhea. There was no difference between the second-line and third-line cabazitaxel-related toxicities (Table 3).

DISCUSSION

Treatment options for mCRPC have expanded in recent years. New generation androgen deprivation therapies, immunotherapy agents and radioactive therapies, as well as a new generation taxane derivative cabazitaxel are also applied in daily practice in the treatment of MCRPC. There are unclear data on the sequential use of these treatment options. At the same time, there are concerns about the safety and efficacy of cabazitaxel after the second-line treatment of this cancer type which especially affects the elderly patients.[10-13] While the median age, visceral and bone metastatis rates of the patients in our study were similar to the previous studies; the rate of the patients with low gleason score (6-7) was

lower than other studies.[14,15]

In the TROPIC study, median PFS with cabazitaxel was reported to be 2.8 months in mCRPC patients after progression on docetaxel.[3] In our study, the median PFS with cabazitaxel was 7.9 months in the second-line treatment with a similar patient group. Prostate-specific antigen (PSA), radiological or clinical progression was sufficient for the definition of progression in the TROPIC study, whereas in our study the time from the onset of cabazitaxel to the PSA increase and clinical or radiological progression was calculated as PFS. Therefore, the PFS difference obtained in our study is due to the difference in the study designs.

In another randomized study published in 2019, cabazitaxel and androgen signal inhibitor were compared in third-line treatment in patients with mCRPC who had progressed on docetaxel and abiraterone or enzalutamide.[8] In this study median PFS was reported 8.0 months in the third-line treatment with cabazitaxel. In our study, the median PFS obtained in the third-line treatment was slightly shorter (5.6 months). PFS was defined as the time from the onset of cabazitaxel to radiological progression, whereas clinical progression was not included in the definition of PFS in this study. The relatively shorter median PFS in third-line treatment with cabazitaxel in our study was thought to be due to this difference of design.

In a retrospective study conducted in Germany to evaluate the efficacy of cabazitaxel in the second and subsequent lines of mCRPC treatment, median PFS with cabazitaxel were reported as 3.9 months in all cohort.[14] In our study, the median PFS in the whole patient group appeared to be better (7.0 months). It was thought that the rate of patients with visceral involvement in our study was lower than the German study led to the difference in median PFS.

In the phase 3 non-inferiority PROSELICA study which 20 mg/m^2 reduced dose and 25 mg/m^2 standard dose cabazitaxel were compared after progression on docetaxel in mCRPC patients, 20 mg/m^2 dose met the non-inferiority criteria.[16] In this study, the median OS obtained with both doses was within the limits of non-inferiority. In our study, approximately half of the patients received cabazitaxel at a dose of 20 mg/m^2, while the other half received standard doses. There was no difference between the two doses in terms of median PFS.

When the patients in our study were stratified according to the gleason score, longer median PFS was obtained with cabazitaxel in patients with higher gleason score (gleason score:9) than those with lower gleason score (gleason score:7-8). This result may be due to the fact that the patient characteristics are not similar in the low and high gleason scores or that the cabazitaxel may be more effective in those with high gleason scores. Similar to this result obtained in our study; according to the TAX-327 study which docetaxel is compared with mitoxtantron, docetaxel shows higher efficacy in high-grade prostate cancer patients than in low-grade patients.[17] From this point of view, it is thought that gleason score can be a predictive marker as well as a prognostic marker. However, there are also negative studies on this subject. In a study on the efficacy of cabazitaxel and predictive factors, gleason score was not seen as a predictive marker for treatment response.[18] Similarly in another study with abireterone acetate, it was shown that gleason score was not a predictive marker for treatment response.[19]

When side effects were evaluated, 87.6% of the patients in our study had any grade cabazitaxel-related adverse event. In previous studies, the incidence of any grade cabazitaxel-related toxicity was reported between 73% and 94%.[3,20]

In the pivotal TROPIC study, primary G-CSF prophylaxis was not administered to patients, and FN was seen in 8% of the patients.[3] In other studies evaluating real-life data, the incidence of FN in cabazitaxel treatment was reported between 3.2% and 8.9%.[8,20,21] Although primary G-CSF was used in almost all of the patients in our study, the incidence of FN was slightly higher (13.6%). The low socioeconomic status of our patients and lack of home care may have caused this.

In both the CAPRISTANA study and another study which investigating the efficacy and safety of cabazitaxel in Canadians, dose delay was reported in about half of the patients.[22] In our study, the frequency of chemotherapy delay was 32.8%. The reason for the relatively low incidence of dose delay in our study may be due to the administration of 20 mg/m^2 cabazitaxel instead of the standard dose in half of our patients.

The limitations of our study are its retrospective nature and the relatively small number of patients. This prevented a strong statistical analysis when investigating factors that may be associated with PFS. However previous studies have often investigated the efficacy and safety of cabazitaxel in the second-line treatment of mCRPC. Our study is one of the rare studies comparing the efficacy and toxicity of cabazitaxel in the second and third-line treatments of mCRPC.

CONCLUSION

Cabazitaxel was found to have similar efficacy in second and third-line treatment of mCRPC in our study. There was no difference between the two group in terms of toxicity. For more definitive results randomized controlled trials involving more patients are needed in this area.

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