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ORIGINAL ARTICLE

Are Hormonal Agents Better Than Chemo in Metastatic Castration-resistant Prostate Cancer?

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OBJECTIVE
In this study, we aim to determine which treatment is more appropriate in castration-resistant chemotherapy-naive patients. Therefore, docetaxel and agents active in the androgen pathway (abiraterone and enzalutamide) were compared retrospectively in patients progressing on androgen deprivation therapy.

METHODS
The study was designed as a retrospective and multicenter study. Patients from five centers in Turkey were included in the study. The primary endpoint of the study was overall survival (OS) and the secondary endpoint was progression-free survival.

RESULTS
Median OS of the docetaxel group was 18.66 months, it was 16.26 months in the hormonal treatment group. There was no statistically significant difference between the groups (p=0.311). Median progression-free survival of the chemotherapy group was 5.6 months, while it was 9 months in the hormonal therapy group. There was statistically significant difference between the groups (p=0.024).

CONCLUSION
There was statistical difference in progression-free survival in favor of hormonal therapies in our study. The difference did not reflect on OS and there was no difference between hormonal therapies and docetaxel. Heterogeneity in the selection of patients is considered to lead to this result; however, larger randomized controlled studies are needed to determine the most appropriate treatment in these patients.

Keywords: Abiraterone; castration resistant; docetaxel; enzalutamide.

Introduction

Androgen deprivation therapy (ADT) alone or in combination with chemotherapy is usually the initial treatment of metastatic castration-sensitive prostate cancer. This treatment creates an objective tumor response in most patients and alleviates symptoms.[1] However, progression is inevitable in these patients and additional treatments are required. The disease is called castration-resistant prostate cancer (CRPC) after developing resistance to ADT. Expected survival rate is low at this level of the disease and patients die substantially due to CRPC.[2,3] Therefore, various agents have been used to treat CRPC. Docetaxel is the first agent used following ADT in this regard. In a study, docetaxel provided overall survival (OS) in patients compared to mitoxantrone.[4] Other agents were used alone or in combination after above-mentioned success of docetaxel, but

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they were not effective.[5-14] Cabazitaxel was found to be effective in patients with CRPC just like docetaxel; however, it was used in post-docetaxel period as it was identified that there was no difference between cabazitaxel and docetaxel in a head-to-head study.[15]

Agents affecting the androgen pathway were also used in CRPC patients. Abiraterone which is an androgen synthesis inhibitor and enzalutamide which is an androgen receptor blocker were used in chemotherapy-naive CRPC patients. Abiraterone was superior to placebo in a study comparing abiraterone with placebo and contributed to both progression-free survival and OS.[16-18] Similarly, enzalutamide was compared with placebo in chemotherapy-naive CRPC patients and it also contributed to progression-free survival and OS.[19-21]

After developing castration resistance, patients have limited response to various treatments; therefore, treatments focused on castration-sensitive period. Chemotherapy and agents active in the androgen pathway are frequently used in combination with ADT in this period. Treatments combined with ADT have become the standard, especially in patients with high disease burden and high risk. However, ADT alone is frequently administered as the initial treatment in metastatic patients. There is no exact information about which treatment should be chosen in these patients after developing castration resistance.

In this study, we aim to determine which treatment is more appropriate in castration-resistant chemotherapy-naive patients. Therefore, docetaxel and agents active in the androgen pathway (abiraterone and enzalutamide) were compared retrospectively in patients progressing on ADT.

Materials and Methods

The study was designed as a retrospective and multicenter study. Patients from five centers in Turkey were included in the study. Files of the patients who applied to these centers between 2016 and 2020 were analyzed and the data were obtained. Inclusion criteria were age >18 years, having metastatic disease, being local treatment naive (surgery or radiotherapy), being chemotherapy naive, and progressing only on ADT. The patients were divided into two groups based on the treatments they received. The first group included those patients who received docetaxel (chemotherapy group). The second group included the patients who received enzalutamide or abiraterone (hormonal therapy group).

OS was defined as the time from the start of second line therapy to death or the last follow-up examination. Progression-free survival was defined as the time from the start of second-line therapy to the date of progression, death, or the last follow-up examination. Tumor progression was evaluated according to the RECIST criteria (only PSA elevation was not accepted as progressive disease). Moreover, following parameters which may affect the survival of the patients were analyzed in Cox regression model: Age (over 65 vs. under 65), location of metastasis (bone only vs. others), Gleason score (9-10 vs. ≤8), and disease burden (high volume vs. low volume-CHAARTED definition). The study was approved by the Manisa Celal Bayar University Faculty of Medicine Ethics Committee (No: 20.478.486, Date: 23/12/2020).

All analyses were performed using the SPSS statistical software program package (SPSS version 20.0 for Windows). The Chi-square test analyzed the differences in the clinical characteristics between the two groups. OS was calculated with the log-rank test. The Kaplan-Meier method was used to draw survival curves. The Cox proportional hazards regression model was used to determine statistically significant variables related to OS. Differences were assumed to be significant when $p<0.05$ was considered.

Results

A total of 80 patients were included in the study. A total of 44 patients received docetaxel and 36 patients received hormonal therapy (abiraterone or enzalutamide). The mean age of patients in the chemotherapy group was 65.5 years (43-82), and it was 71.5 years in the hormonal therapy group (48-96). The mean follow-up duration was 20.4 months for chemotherapy group and 15.6 months for hormonal therapy group. When the distribution rates of age, location of metastasis, Gleason score, and disease burden parameters in the groups were analyzed, it was found that only patients over 65 years of age were statistically higher in the hormonal treatment group. The characteristics of the patients are shown in Table 1.

The effect of these four variables (age, location of metastasis, Gleason score, and disease burden) on the survival of all patients was also studied in in the multivariate analysis. Among these variables, only the Gleason score had a statistically significant effect on the survival ($p=0.029$) (Table 2).

Median OS of the chemotherapy group was 18.66 months, it was 16.26 months in the hormonal treat-

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Table 1 General characteristics of patients

Patients	Docetaxel (n=44)	Enzalutamide or abiraterone (n=36)
Age		
p=0.042	65.5 (43-82)	71.5 (48-96)
Gleason 9-10		
p=0.341	24	17
Bone only disease		
p=0.499	28	22
Visceral disease	4	3
Volume (CHAARTED definition)		
High volume	15	8
Low volume	29	28
p=0.179		
Mean follow-up duration (month)	20.4	15.6

CHAARTED: Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer Study

Table 2 Cox regression

All Patients	Sig.(p)	Hazard ratio
Age	0.102	1.749
Gleason_score	0.029	0.528
Location_of_metastasis	0.738	0.904
Disease_burden	0.529	0.812

Sig.: Parameters which may affect the survival (significant when the p<0.05)

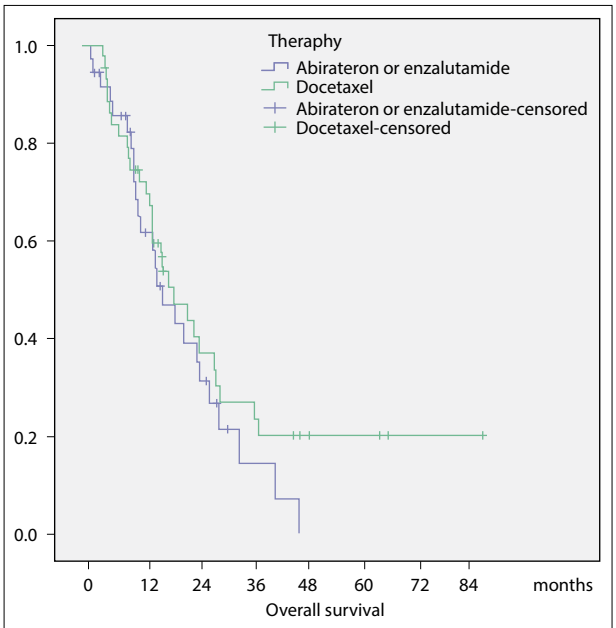

Fig. 1. Overall survival of patients.

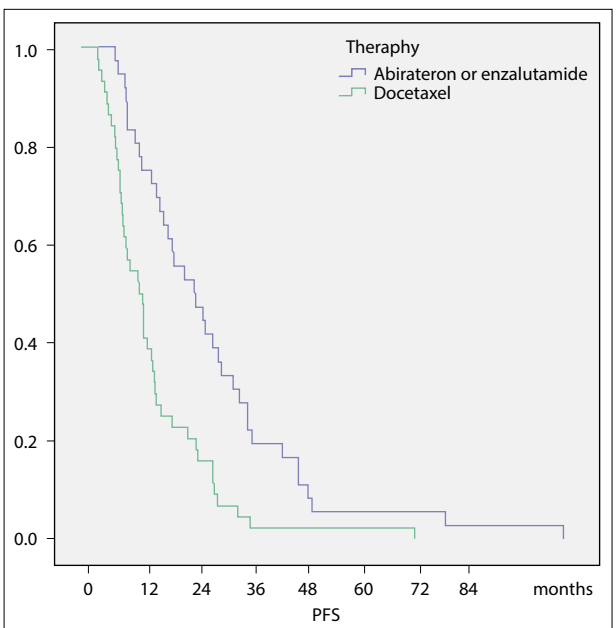

Fig. 2. Progression free survival of patients.
PFS: Progression free survival.

ment group. There was no statistically significant difference between the groups (p=0.311). OS data are shown in Figure 1. A total of 15 patients in the chemotherapy group and 11 patients in the hormonal treatment group were alive at the time of data entry.

Median progression-free survival of the chemotherapy group was 5.6 months, while it was 9 months in the hormonal therapy group. There was statistically significant difference between the groups (p=0.024). Progression-free survival data are shown in Figure 2. Nine patients in the hormonal therapy group and three patients in the chemotherapy group were still on their treatment at the time of data entry.

Discussion

It is not clear which agent should be used in the treatment of metastatic castration-resistant chemotherapy-naive patients. Many options have been evaluated until today; docetaxel has become prominent as treatment of choice for chemotherapy, while abiraterone and enzalutamide have become the hormonal treatments of choice. There is no prospective study on these agents; therefore, the treatment of these patients is up to the clinicians' decision.

When we examined the studies of these agents in CRPC patients, in a Phase 3 randomized study, where docetaxel, which was the first agent used, was com-

pared with mitoxantrone, median survival in patients who received docetaxel was found to be 18.9 months.[4] In a study on abiraterone in this population, median survival was 34.7 months.[17] In another study on enzalutamide in CRPC patients, OS was found to be 35.3 months.[21]

In the present study, the OS of docetaxel was 18.66 months, and it was 16.26 months for abiraterone and enzalutamide which are hormonal therapies. In the numerical analysis of the results, the survival of the patients in the docetaxel arm was almost the same as the pivotal study.[4] However, this was not the case for the patients taking enzalutamide and abiraterone. The OS of these agents with an OS of 34 months in their pivotal study was 16.26 months in the present study. This may be due to the difference in the selection of patients. In pivotal studies of these agents, asymptomatic patients were especially included. As there were no such selection criteria in our study, it may have resulted in the difference. In Turkey, where the present study was conducted, abiraterone or enzalutamide can be used in patients who are not suitable for chemotherapy. Therefore, patients whose general condition is relatively worse receive hormonal therapies. The age parameter was significantly in favor of hormonal therapies and this result also promotes the condition. OS may be low in our study due to this disadvantage in patient selection. Poor survival in the pivotal study of docetaxel may result from not using other agents, which prolong life time, in sequential therapy.

In our study, progression-free survival was statistically significantly higher in the hormonal therapy arm than the group receiving chemotherapy. Despite the above-mentioned disadvantage in the selection of the patients, hormonal therapies were successful in progression-free survival compared to chemotherapy; however, the difference did not reflect on OS. This success in progression-free survival, on the other hand, obtained despite the limited number of patients. Therefore, based on the results of our study, hormonal therapies (abiraterone or enzalutamide) are more successful than docetaxel in castration-resistant metastatic chemotherapy-naive patients. Nevertheless, it is not possible to reach a definite conclusion based on the results of our retrospective study and larger prospective randomized controlled studies are needed on this subject.

Conclusion

There is no consensus on which drugs should be administered in chemotherapy-naive patients with metastatic castration-resistant prostate cancer. There was a statistical difference in progression-free survival in favor of hormonal therapies in our study. The difference did not reflect on OS and there was no difference between hormonal therapies and docetaxel. Heterogeneity in the selection of patients is considered to lead to this result; however, larger randomized controlled studies are needed to determine the most appropriate treatment in these patients.

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Ethics Committee Approval: The study was approved by the Manisa Celal Bayar University Faculty of Medicine Ethics Committee (No: 20.478.486, Date: 23/12/2020).

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