Are Hormonal Agents Better Than Chemo In Metastatic Castration Resistant Prostate Cancer?

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Abstract

INTRODUCTION

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

MATERIAL METHOD

The study was designed as a retrospective and multi-center study. Patients from 5 centers in Turkey were included in the study. The primary endpoint of the study was overall survival and the secondary endpoint was progression-free survival.

RESULTS

Median overall survival of the chemotherapy 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 overall survival 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.

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 in patients compared to mitoxantrone (4). Other agents were used alone or in combination after above-mentioned success of docetaxel, but 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 overall survival (16-18). Similarly, enzalutamide was compared with placebo in chemotherapy-naive CRPC patients and it also contributed to progression-free survival and overall survival (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 multi-center study. Patients from 5 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 for metastatic diseases, 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).

The primary endpoint of the study was overall survival and the secondary endpoint was progression-free survival. Overall survival was identified as the period from the initiation of a second-line therapy to the date of death or the last visit date. Progression-free survival was identified as the period from the initiation of a second-line therapy to progression or the last visit date. Moreover, following parameters which may affect the survival of the patients were analyzed: age, location of metastasis and Gleason score. Our study was conducted as per the Declaration of Helsinki and performed with the approval of the Manisa Celal Bayar University Medical School Ethics Committee. Informed consent was obtained from all subjects.

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 the p-value of less than 0.05.

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 44 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 difference between the two groups was studied considering the age limit of 65 years. The rates of the patients over 65 years old were statistically significantly higher in the hormonal therapy arm ($p = 0.042$). The chemotherapy group included 28 patients with bone metastasis only and four patients had visceral metastasis based on the location of metastasis. In the hormonal therapy group, there were 22 patients with bone metastasis only and three patients had visceral metastasis. There was no significant difference between the groups in the rates of the patients with bone metastasis only ($p = 0.499$). When the chemotherapy group was evaluated according to Gleason score, there were 19 patients with a Gleason score of eight or less and 24 patients were with a Gleason score of nine or 10. The numbers of the patients in the hormonal therapy group were 17 and 18, respectively. When the rates of the patients with a Gleason score of 9-10, there was no statistical difference between the groups ($p = 0.341$). The characteristics of the patients are shown in Table 1.

The effect of these three variables (age, location of metastasis, and Gleason score) on the survival of all patients was also studied regardless of the groups. Among these variables, only the Gleason score had a statistically significant effect on the survival (Gleason ≤ 8 vs Gleason 9-10, 23.37 vs 14.93 months) ($p = 0.03$) (Figure 1).

Median overall survival of the chemotherapy group was 18.66 months, it was 16.26 months in the hormonal treatment group. There was no statistically significant difference between the groups ($p = 0.311$). Overall survival data are shown in Figure 2. 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 3. Nine patients in the hormonal therapy group and three patient in the chemotherapy group was 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-naïve 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 compared 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, overall survival was found to be 35.3 months (21).

In the present study, the overall survival 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 that of the pivotal study (4). However, this was not the case for the patients taking enzalutamide and abiraterone. The overall survival of these agents with an overall survival 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 was 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. Overall survival 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 overall survival. 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 statistical difference in progression-free survival in favor of hormonal therapies in our study. The difference did not reflect on overall survival 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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Tables

Table 1-

	Docetaxel (n=44)	Enzalutamid or Abirateron (n=36)
Age	65.5 (43-82)	71.5 (48-96)
<i>p</i> =0.042		
Gleason 9-10	24	17
<i>p</i> =0.341		
Bone Only Disease	28	22
<i>p</i> =0.499		
Visseral Disease	4	3

General characteristics of patients

Figures

Figure 1

Overall survival curves of the patients according to the Gleason score

Figure 2

Overall survival curves of the patients according to therapy

Figure 3

Progression free survival curves of the patients according to therapy