Effect of Upfront Docetaxel in *De Novo* Metastatic Castration-Sensitive Prostate Cancer Patients with Gleason Grade Group 5

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ABSTRACT

Objective: To investigate whether adding docetaxel chemotherapy to androgen deprivation therapy is effective regarding progression-free and overall survival in patients with *de novo* metastatic castration-sensitive prostate cancer patients with Gleason Grade Group 5 (Gleason scores 9 and 10).

Study Design: Observational study.

Place and Duration of the Study: Department of Medical Oncology at Manisa Celal Bayar University, Izmir Ege University, Bitlis Tatvan Public Hospital, Izmir Bozyaka Education and Research Hospital, and Izmir Kent Hospital, from March 2015 to May 2020.

Methodology: Patients with *de novo* metastatic castration-sensitive and histopathologically confirmed GGG 5 prostate cancer were evaluated retrospectively. The patients were divided into two groups. The first group included patients who were given androgen deprivation therapy alone (ADT-only group), and the second group consisted of patients who were given ADT plus docetaxel (chemohormonal group). The two groups were compared in terms of overall survival and progression-free survival till cut-off limit.

Results: A total of 194 patients with metastatic castration-sensitive and GGG 5 prostate cancer were analysed retrospectively. The chemohormonal group comprised of 72 patients, and the ADT-only group included 122 patients. Median progression-free survival was 15.7 months in the chemohormonal group and 14.8 months in the ADT-only group ($p = 0.97$). The median overall survival was 37.5 months in the chemohormonal group and 37.8 months in the ADT-only group ($p = 0.93$).

Conclusion: The addition of docetaxel chemotherapy in patients with metastatic castration-sensitive and GGG 5 prostate cancer did not result in a statistically significant difference in terms of overall survival and progression-free survival. Docetaxel may be ineffective in this group of patients.

Key Words: *Prostate cancer, Castration-sensitive, Gleason grade group 5, Docetaxel, Androgen deprivation therapy (ADT), Overall survival.*

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INTRODUCTION

Since its inception, the Gleason grade system has been an important basis for clinical decision-making in patients with prostate cancer.[1] It is based on the differentiation status of prostate cancer cells and is closely related to prognosis. A higher score indicates less differentiated tumours and therefore a worse prognosis.[2] Based on the degree of differentiation and growth pattern, prostate cancers are graded from 1 to 5, grade 5 being the least differentiated.[3] The Gleason score is the sum of the two most prevalent patterns (i.e. the primary and secondary grades).

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The International Society of Urological Pathology (ISUP) established a new classification system in 2014. The system comprises of five different Gleason grade groups (GGG), Where GGG 1 indicates a Gleason score ≤6, GGG 2 a Gleason score 3+4=7, GGG 3 a Gleason score 4+3=7, GGG 4 a Gleason score = 8 (which include 4+4 = 8, 3+5 = 8, or 5+3 = 8) and GGG 5 Gleason scores 9 to 10 (namely 4+5, 5+4, or 5+5).[4] In subsequent studies, it was shown that the GGG 5 patients had worse prognosis than the GGG 4 patient group.[5,6]

Docetaxel and androgen deprivation therapy (ADT), also called the chemohormonal approach, is one of the standard therapies in patients with metastatic castration-sensitive prostate cancer (mCSPC) with a high disease burden. Several phase 3 studies have shown the efficacy of the chemohormonal approach.[7-10] In these studies, the patients were classified according to their Gleason scores and divided into two groups: Gleason scores ≤7 and ≥8. The chemohormonal approach was found to be efficient in all the patients, but in the Gleason ≥8 subgroup, this effect was found to be less. A meta-analysis indicated that as Gleason

scores decrease, the efficacy of the chemohormonal approach becomes greater.[11] Accordingly, in patients with GGG 5, the effect may be less. No studies have evaluated the efficacy of chemohormonal therapy only in patients with metastatic castration-sensitive GGG 5 prostate cancer. This study aimed to compare the effectiveness of ADT with or without docetaxel in patients with *de novo* metastatic GGG5 prostate cancer.

METHODOLOGY

Prostate cancer patients admitted to medical oncology departments of Manisa Celal Bayar University, Izmir Ege University, Bitlis Tatvan Public Hospital, Izmir Bozyaka Education and Research Hospital, and Izmir Kent Hospital, between March 2015 and May 2020 were screened in this retrospective multicentre study. Patients with *de novo* metastatic and histopathologically confirmed GGG 5 prostate cancer, aged ≥18, with an ECOG (Eastern Cooperative Oncology Group) score of 0 - 2 at diagnosis, and no prior local therapy (surgery or radiotherapy) for prostate cancer were included in the study. Patients who had relapsed after local treatment or had castration-resistant disease on admission to the centres were excluded from the study. The data of each suitable patient were carefully recorded from the hospital medical records or written archived files.

Patients were classified into two groups according to the first line therapy received during mCSPC treatment. The first group included patients who were given ADT alone (ADT-only group), and the second group comprised patients who were given ADT plus docetaxel (docetaxel 75 mg/m^2 once in 21 days with an average of six cycles; chemohormonal group). The patients who received combined androgen blockade therapy were also included in the ADT-only group. The treating physician had decided whether the patients would receive ADT alone or combined with docetaxel.

The two groups were compared regarding overall survival (OS) and progression-free survival (PFS). OS was defined as the time from the start of first-line therapy to death or the last follow-up examination, while PFS was defined as the time from the beginning of the first-line treatment to the date of progression (data cut-off in May 2020). Tumour progression was evaluated according to the RECIST criteria (i.e. PSA elevation alone was not accepted as an indication of progressive disease because there is no specific standard for PSA progression in metastatic diseases).

The effects of age (over and under 65 years), metastatic site (bone-only disease, visceral disease, and lymph node-only disease), ECOG performance score (0–1 and 2), baseline PSA, disease burden (low and high) and upfront docetaxel on OS were examined. The level of disease burden was determined according to the criteria used in the CHAARTED study. A high disease burden was defined as the presence of visceral metastases or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis.[8] A univariate analysis was performed on these variables. A multivariate analysis was then performed with the parameters with significant efficacy. The study was conducted as per the Declaration of Helsinki and received approval from the local ethics committee at Manisa Celal Bayar University.

All the analyses were performed using SPSS version 20.0 for Windows. The Chi-square test was used to determine the differences in the two groups' clinical characteristics. The OS and PFS were calculated using the log-rank test. The Kaplan–Meier method was used for drawing survival curves. The univariate and multivariate analyses were conducted with Cox-regression models using hazard ratios and 95% CI. The differences were considered statistically significant when the p-value was less than 0.05.

RESULTS

A total of 194 mCSPC patients with GGG 5 (Gleason scores of 9 or 10) who were treated during the period of 2015 to 2020 were analysed retrospectively. Of the patients, 72 were given docetaxel plus ADT (chemohormonal group), and 122 were given ADT alone (ADT-only group). The patients' characteristics are presented in Table I.

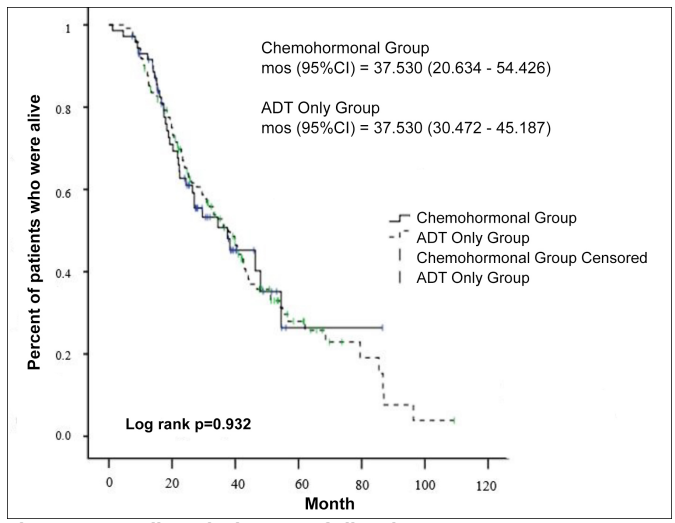

Figure 1: Overall survival curves of all patients.

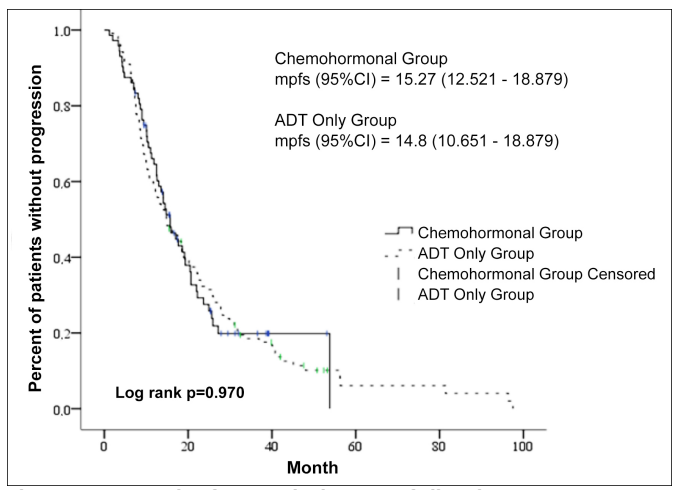

Figure 2: Progression free survival curves of all patients.

Table I: General characteristics of patients.

	Overall n=194	ADT only group n=122	Chemohormonal group n=72	p * (Chi-square)
Age				
Median (range) — year	68 (43-85)	70 (43-85)	65 (47-80)	
<65 years — no. (%)	38.7	31.1	51.4	0.004
Performance status				
ECOG 0-1 — no. (%)	178 (91.8)	109 (89.3)	69 (95.8)	
ECOG 2 — no. (%)	16 (8.2)	13 (10.7)	3 (4.2)	0.09
Volume **				
High — no. (%)	165 (85.1)	105 (86.3)	60 (83.3)	
Low — no. (%)	19 (14.9)	17 (13.7)	12 (16.7)	0.375
Gleason score				
9 — no. (%)	116 (59.8)	77 (63.1)	39 (54.2)	
10 — no. (%)	78 (40.2)	45 (36.9)	33 (45.8)	0.141
Metastatic site				
Bone only — no. (%)	73 (37.6)	57 (46.7)	16 (22.2)	<0.001.020
Visseral — no. (%)	33 (17)	15 (12.5)	18 (25)	0.127
Lymph node only — no. (%)	8 (4.1)	3 (2.5)	5 (6.9)	
PSA (beginning ADT) — mean ng/ml	411 (5-7900)	462 (6-7900)	322 (5-2848)	0.326
ALP (beginning ADT) — mean IU/L	313(41-2539)	320(41-2539)	303(50-1142)	0.779
Time from ADT to docetaxel — mean-month	-	-	2.87 (0.4-8)	
Cycles of docetaxel-mean	-	-	6.18 (2-11)	
Follow up duration-month	31.54	34.2	26.8	

** Statistical difference between the two groups in terms of the variable.*
*** The level of disease burden was determined according to the criteria used in the CHAARTED study.*

Table II: Univariate and multivariate analysis for overall survival.

Univariate	p	HR	95%	CI
Age	0.080	0.707	0.480	1.043
ECOG	0.654	0.872	0.479	1.578
Baseline PSA	0.839	1.000	1.000	1.000
Visceral disease	0.467	0.835	0.514	1.357
Bone only disease	0.771	1.057	0.729	1.531
Lymph node only disease	0.059	6.661	0.930	47.736
Disease burden	0.006	0.438	0.245	0.785
Upfront docetaxel	0.932	1.018	0.680	1.524
Age	0.098	0.721	0.489	1.062
Lymph node only disease	0.113	4.956	0.685	35.884
Disease burden	0.017	0.487	0.271	0.878

The median OS was 37.5 months for the chemohormonal group and 37.8 months for the ADT-only group (p = 0.932). There was no statistically significant difference between the two groups regarding OS (Figure 1). The median PFS was 15.7 months for the chemohormonal group and 14.8 months for the ADT-only group (p = 0.97, Figure 2).

Three of the variables were selected for the study based on their p-values (age, lymph-node-only disease and disease burden). The multivariate analysis was performed with these three parameters. On multivariable analysis, only disease burden was found to have a statistically significant impact on OS (Table II). No statistically significant differences in the distribution of the patients with a low disease burden were found between the groups (p = 0.37).

After disease progression, 62 out of 72 patients in the chemohormonal group (86%) and 108 out of 122 patients in the ADT-only group (89%) received second-line therapy. In the chemohormonal group, 57 out of 62 patients received abiraterone or enzalutamide. In the ADT-only group, 88 patients received docetaxel, and 20 patients received abiraterone or enzalutamide in the second line; 78 out of 88 patients who received docetaxel also received abiraterone or enzalutamide in the third-line therapy.

DISCUSSION

Three large randomised trials found the chemohormonal approach superior to ADT alone for the treatment of mCSPC and subsequently became the standard treatment. Although effective in all the patient subgroups in these trials, the chemohormonal approach was more effective in patients with a high disease burden. The patients in such studies were also classified and analysed according to their Gleason scores. In the CHAARTED trial, the patients with Gleason scores of ≤7 and ≥8 were examined. The addition of docetaxel to ADT provided a significant difference in OS in both subgroups. However, the hazard ratio of the subgroup with a Gleason score ≤7 was 0.41, while that of the subgroup with a Gleason score ≥8 was 0.60.[8]

In the STAMPEDE trial, the patients were also evaluated in two subgroups with Gleason scores of ≤7 and ≥8. Although the standard therapy (ADT only) and chemohormonal approach were found to be efficient in both subgroups, there was a difference in the hazard ratios (0.67 for the patients with a Gleason score ≤7 patients *vs.* 0.76 for patients with a Gleason score ≥8).[9] Another randomised study that used the chemohormonal approach was the GETUG-15 trial. As in the other studies, patients were examined in two subgroups with a Gleason score of ≤7 and a Gleason score of ≥8. Although no difference in OS was found in this trial, the hazard ratio of

the subgroup with a Gleason score ≤7 was 0.71, while the hazard ratio in the subgroup with a Gleason score ≥8 was 1.27.[10]

These three large studies evaluated the GGG 4 and GGG 5 patients altogether. However, the GGG 4 and GGG 5 patient groups differed from one another in terms of prognosis. In 2013, Pierorazio *et al*. showed the survival data of 7850 operated prostate cancer patients in their study. The recurrence-free survival was 63.1 and 34.5% in men with GGG 5 and in patients with GGG 4, respectively.[12] In 2017, Tsao *et al.* published an analysis of a GGG 4 and GGG 5 prostatectomy cohort of 847 prostate cancer patients.[6] In this cohort, the patients with Gleason scores of 9-10 had the worst survival. OS of those with Gleason 9-10 disease was shorter than for Gleason 8 disease regardless of the treatment (usually more aggressive treatments).

GGG 4 and GGG 5 are heterogeneous groups. GGG 4 includes patients with Gleason scores of 4+4, 3+5, 5+3, while GGG 5 includes patients with Gleason scores of 4+5, 5+4, 5+5. In some studies, a prognostic difference had been noted even in the subgroups of the GGG 4 patient population. Mahal *et al.* showed that the overall survival of patients with a Gleason score of 3 + 5 = 8 and 4 + 4 = 8 was similar, but patients with a Gleason score of 5 + 3 = 8 had a shorter overall survival than the other two subgroups. For this reason, it was recommended that the patient group with Gleason score of 5 + 3 = 8 had a prognosis like the GGG 5 patient group and that follow-up-treatment should be performed according to this situation.[13] Since the prognostic difference was evident even in the GGG 4 patient subgroups, it is clear that evaluating all GGG 4 and GGG 5 patients together will not yield accurate results.

When all the aforementioned studies were reviewed together, it was evident that docetaxel added to ADT was less effective in GGG 4 and GGG 5 patients than others. There were also significant differences in the prognoses between GGG 4 and GGG 5 patients. For this reason, the authors surmised that the evaluation of the GGG 5 patient group alone would provide more accurate results.

In this study, adding docetaxel to ADT did not make any difference regarding OS and PFS in patients with GGG 5. Using docetaxel in the GGG 5 patients had no effect other than toxicity. Recent studies had shown that adding abiraterone or darolutamide to docetaxel and ADT treatment in mCSPC patients can prolong OS and hence, docetaxel had become one of the standard treatment in these patients.[14,15] The efficacy of docetaxel in the treatment of GGG 5 prostate cancer patients should be demonstrated in large-scale randomised trials. If the results are found to be similar to those in this study, it would be appropriate to give ADT together with abiraterone, enzalutamide or darolutamide to treat these patients, and in the case of progression, alternatives other than chemotherapy (especially with Lutetium Lu 177) may be considered.

The treatments received by the patients following progression were also examined in this study. ADT, docetaxel, and hormonal agents (i.e. abiraterone or enzalutamide), which had been shown to prolong life in metastatic prostate cancer, were received by 79.16% of the patients in the chemohormonal group and 73.77% of the ADT-only group.

This study had some limitations. First, the study was retrospective with no homogeneity in the patient selection. The distribution of the two groups of patients with ECOG scores of 2, those with bone-only disease, those with visceral disease, and those with lymph-node-only disease showed heterogeneity. Another limitation of the study was the low number of patients that were included. In addition, more patients received the ADT treatment alone than those who received the combined treatment, and treatment with docetaxel was even less. In a study conducted in 2020, Swami *et al.* found that treatments known to prolong life in patients with prostate cancer were used less frequently, and the reasons for this were determined to be insurance, cost, access, fear of toxicity (financial and drug related), patients age, comorbid diseases, and social problems.[16] The present reasons were similar. Docetaxel has also been used in low-volume disease and appears to be used in low-volume patients. The reason for this is thought to be the preference of the physicians. Despite these limitations, to the best of authors' knowledge, this study is the first to involve real-life data of mCSPC patients with GGG 5 in which ADT alone was compared with the chemohormonal approach. This research is essential because of its results. More extensive randomised studies on a similar population are though needed.

CONCLUSION

Adding docetaxel to ADT treatment did not provide a statistically significant difference in OS and PFS in patients with metastatic castration-sensitive GGG 5 prostate cancer. The results of large randomised clinical studies or meta-analyses should be awaited before administering docetaxel chemotherapy to patients with GGG 5 prostate cancer.

ETHICAL APPROVAL:
An ethical approval was taken from the Ethical Review Committee of Manisa Celal Bayar University (ERC/ID/141 dated 22.03.2021) prior to the initiation of research work.

PATIENTS' CONSENT:
Informed written consents were taken from all the subjects prior to the initiation of research work.

COMPETING INTEREST:
The authors declared no competing interest.

AUTHORS' CONTRIBUTION:
SY: Data collection and analysis, and manuscript drafting.
CY: Data interpretation and analysis, manuscript revision and drafting.
All authors approved the final version of the manuscript to be published.

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