Comparison of Weekly Low Dose Docetaxel with the Standard Protocol in Hormone-resistant Metastatic Prostate Cancer

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ABSTRACT

Objective: To evaluate and compare the effects and toxicity of weekly low dose with three weekly standard doses of docetaxel in hormone-resistant metastatic prostate cancer.

Study Design: Descriptive study.

Place and Duration of Study: University of Health Sciences, Ankara Training and Research Hospital, Ankara, Turkey, from January 2013 to July 2021.

Methodology: The study was conducted on 79 patients with refractory prostate cancer. Patients were assessed in 2 groups. One group was treated with the classical standard Docetaxel dose 75 mg/m^2/day (every 3-week) + Prednisolone 10 mg/day (daily), whereas the second group consisting of elderly and poor performance status received a low dose Docetaxel 25 mg/m^2/day (weekly, 1-week interval) + Prednisolone 10 mg/day (daily).

Results: The overall survival and toxicity profile differences between the low dose protocol in this study and the standard treatment protocol were compared. Survival times in both groups were found as 44.3 months and 35.5 months in 1-week and 3-week interval groups, respectively (p = 0.09). The rate of hematologic toxicity associated with systemic treatment was 10% in the 1-week interval treatment group and 41% in the 3-week group (p = 0.002). In particular, the febrile neutropenia was 30.8% in the 3-week interval group and 2.5% (p = 0.001) in the 1-week interval group.

Conclusion: The study showed that instead of using docetaxel in the standard dose and range, it is more tolerated in elderly and poor performance patients when administered in the revised dose. The disrupting effects of chemotherapy are overperforming, especially in such patients.

Key Words: *Metastatic prostate cancer, Hormone resistant prostate cancer, Weekly docetaxel.*

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INTRODUCTION

Prostate cancer is the most common type of cancer in men. It ranks second after lung cancer as a cause of death from cancer. When diagnosed with prostate cancer, 30% of the patients are in the metastatic stage. Twenty-five percent of the patients also develop metastasis in the following years after diagnosis. Ninety percent of patients have bone metastases, causing serious pain. In 35% of the patients, soft tissue metastases occur, while lymph node metastases occur in 20% of the patients.

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Due to the high frequency of bone metastases, complications including skeletal and vertebral fractures are responsible for a significant proportion of patient morbidity.[1,2] The survival rate in metastatic prostate cancers is longer than in other metastatic cancers. This is because prostate cancer is very sensitive to hormone therapy. Ninety percent of newly diagnosed patients with prostate cancer are treated by hormone therapy alone (LHRH, Luteinizing Hormone-Releasing Hormone). Patients experience progress in about 3 years.[1-4]

The chances of early diagnosis and radical treatment have increased with the increased use of Prostate Specific Antigen (PSA) used in the follow-up of patients. Thus, the rates of disease-related mortality have remarkably decreased.[1-4]

Hormone-resistant prostate cancer (HRPC) is characterised by an increase in PSA or progression of the disease radiologically or clinically, although serum testosterone levels are below 50 ng/dl.[2]

Patients with hormone-resistance in the metastatic phase of prostate cancer need to undergo chemotherapy. The Docetaxel (75 mg/m^2) + Prednisolone (10mg/daily) chemotherapy protocol,

a form of systemic treatment, was approved firstly by the American Food and Drug Administration (FDA) and continued to be used as a standard since 2004, is implemented as one cycle per 21 days, between 6-8 cycle in total.[3,4]

Docetaxel is a taxane that blocks microtubule activity that leads to apoptosis during cell division.[5]

Since the initial STAMPEDE report, first-line systemic combination treatment options given with ADT in metastatic hormone-sensitive prostate cancer (mHSPC) have expanded to include abiraterone, enzalutamide, apalutamide as well as docetaxel.[6-9] However, there is still controversy about patients' stratification and selection of treatment.[10-13]

In addition to chemotherapy agents, targeted hormone drugs (abiraterone, enzalutamide, *etc*.) have been approved in the world and the authors' country for the treatment of metastatic prostate cancer. But as much as the effect of docetaxel treatment, which is still the most up-to-date treatment, it causes some problems such as discontinuation of treatment, hospitalisation, and fatigue because of its toxic effects. The most common side effect of Docetaxel is myelosuppression. Allergic reactions related to docetaxel occur in 15% of the patients.

It is becoming impossible to treat patients because of these toxic effects, especially in the patient group with advanced age and ECOG performance status of 1 or 2. Most patients are forced to stop their treatment due to these toxic effects. The authors are trying to extend the life expectancy of patients with this condition and find a way to use it without undermining the comfort of the patient. The side effects of Docetaxel therapy are more pronounced in the elderly and patients with low-performance status. The aim of this study was to evaluate and compare the effects and toxicity of weekly low doses with three weekly standard dose of docetaxel in hormone-resistant metastatic prostate cancer of elderly patients with poor performance status.

METHODOLOGY

The files of patients with metastatic hormone-resistant prostate cancer, who were followed up and treated between January 2013 and July 2021 at Ankara Education and Research Hospital Oncology Clinic, were retrieved. Patients were divided into two groups according to the treatment given.

In one group of these patients (39 patients), the standard form of treatment, Docetaxel (75 mg/m^2/day) + Prednisolone (10mg/every day) chemotherapy protocol, was administered once every 21 days to a total of 6-8 cycles. General inclusion criteria in this group were patients under 70 years of age and ECOG zero (0-1) performance status or patients over 70 years of age and ECOG zero (0) performance status.

In the experimental group (40 patients), Docetaxel (25 mg/m^2/day) + Prednisolone (10 mg/every day) combination was administered every 7 days. Patients, who underwent 3 weeks of chemotherapy, were given rest for 1 week. They underwent a total of 6-8 cycles of chemotherapy (18-24 sessions, where 3 weekly sessions constituted 1 cycle). General inclusion criteria in this group were patients over 70 years of age and ECOG 0-2 performance status or patients under 70 years of age and ECOG 1-2 performance status.

General exclusion criteria was patients with non-metastatic prostate cancer (Stage 1, 2, 3), hormone-sensitive patients, and patients who received chemotherapy other than Docetaxel, next-generation hormone agents (Abiraterone, Enzalutamide) patients with ECOG performance scores of 3 and 4, and those with uncontrolled Diabetes (as prednisolone use is contraindicated) were also excluded.

All patients underwent biochemical blood tests, complete blood count, urine test, total PSA, free PSA, total testosterone, cardiac and neurological examinations, and PSMA-PET before starting treatment. All the tests were repeated at the end of treatment. The results were compared.

In addition, patients were followed up with biochemical blood tests and complete blood counts before each treatment session.

ECOG (WHO-Zubrod Performance Scale) is a scale that was used to evaluate the overall well-being of cancer patients.[14]

LHRH analogues such as Goserelin, and leuprolide acetate were used as androgen ablation methods. Orchiectomy was performed as surgical ablation. The total testosterone levels of all patients were below 20 ng/dl.[15-17]

Statistical analysis was done using SPSS 25 and Microsoft Office Excel 2007. Shapiro-Wilk test was used for normality analysis of the groups. It was found that the 3-week group was not normally distributed, and the survival times of the 1-week treatment group were normally distributed (3-week $p = 0.011$, 1-week $p = 0.253$). For this reason, the authors applied the Mann-Whitney U-test, which is a non-parametric test. Pearson's chi-square or Fisher's exact test was used to compare the differences between the groups. A p-value of <0.05 was considered statistically significant.

RESULTS

The docetaxel treatment given every 3 weeks in this study caused some side effects. The age of the patients ranged between 51 years and 79 years with an average of 67.2 years. There were no patients at age 81 years and older. The patients were mostly in the 61-70 age group (64%). There were only 10 patients over the age of 70 (25.6%).

The age of the patients ranged between 57 years and 89 years with an average of 77.3 years in the weekly docetaxel treatment. Forty percent of patients were aged 81years and older. Thirty-three patients were over 70 years old (82.5%).

Group distributions of the patients by age and ECOG performance are also given in Table I.

Table I: Clinicopathological characteristics.

	3-week treatment group	1-week treatment group
Number of patients	39	40
AGE distribution (years)		
60 and below	4 (10.3%)	2 (5%)
61-70	25 (64.1%)	5 (12.5%)
71-80	10 (25.6%)	17 (42.5%)
81 and over	0	16 (40%)
Metastases		
Bone	38 (97.4%)	39 (97.5%)
Soft tissue	5 (12.8%)	5 (12.5%)
Bone + soft tissue	5 (12.8%)	5 (12.5%)
Lymph nodes	13 (33.3%)	12 (30%)
Bone + lymph nodes	12 (30.8%)	11 (27.5%)
Soft tissue + lymph nodes	5 (12.8%)	3 (7.5%)
Bone + lymph nodes + soft tissue	5 (12.8%)	4 (10%)
Gleason score		
7 and below	5 (12.8%)	5 (12.5%)
8 and over	34 (87.2%)	35 (87.5%)
ECOG performance status		
ECOG 0	35 (89.7%)	8 (20%)
ECOG 1 and 2	4 (10.3%)	32 (80%)
PSA level first		
PSA 25 and below	0	2 (5%)
PSA 26-70	9 (23%)	17 (42.5%)
PSA 71-160	20 (51.3%)	13 (32.5%)
PSA 161-497	6 (15.4%)	6 (15%)
PSA 498 and above	4 (10.3%)	2 (5%)

PSA: Prostate specific antigen levels.

Table II: Toxicity in the groups.

	3-week treatment group	1-week treatment group
Cardiac toxicity	2 (5%)	0
Hematological toxicity	16 (41%)	4 (10%)
Febrile neutropenia	12 (30.8%)	1 (2.5%)
Admission to hospital	11 (28%)	0
Fatigue	35 (89.7%)	2 (5%)
Request to stop treatment	18 (46%)	1 (2.5%)
Dosage reduction (70mg/m^2/day)	14 (35.9%)	0
Dosage reduction 60mg/m^2/day)	2 (5%)	0
Neuropathy	4 (10.3%)	4 (10%)
Going to the hospital	4 (10.3%)	18(45%)
Analgesic discontinuation	14 (36%)	14 (35%)
Analgesics reduction	25 (64%)	26 (65%)

All the patients completed the treatment despite advanced age and poor ECOG performance. All the files were examined, and the proportions of toxicities seen during treatment are detailed in Table II.

Response of disease and statistical distributions was examined at the end of the treatment based on the groups and indicated in Table III.

In the three-weekly group, the number of patients with ECOG performance scores of 1 and 2 was 4 (10%). In 12 of the patients, febrile neutropenia (30.8%) was observed, while the number of patients who required hospitalisation was 11 (28.2%). Hematological side effects were mostly neutropenia (74%) followed by thrombocytopenia (14%) and anemia (12%).

Cardiovascular toxicity was observed in 2 of the patients. In patients whose ejection fraction (EF) decreased, after a break of 2 weeks, the EF rates again rose above 60 and the treatment was continued. Neuropathy developed in only 4 patients (10.3%). All patients' complaints were recovered during their long-term follow-up.

Due to the toxicity, the request to discontinue the treatment was approximately 46%. A dose reduction was made in 41% of the patients. The percentage of patients, who completed the treatment with a dose decreased from 75 mg/m^2/day to 70 mg/m^2/day, was 36%, while patients, who completed the treatment with a dose decreased from 75 mg/m^2/day to 60 mg/m^2/day, was just 5%.

All the patients' pain disappeared or decreased. The analgesic discontinuation was observed in 36%. Another 64% said their need for analgesics had decreased.

Patients' fatigue, weakness, and lack of appetite were observed in 90%. The most common complaint of patients, who requested to discontinue the treatment, was fatigue. That was the side effect most cited as the reason for discontinuing treatment (Tables I-II).

The number of patients with ECOG performance status in weekly docetaxel treatment groups 1 and 2 was 32 (80%).

There was no hospitalisation in this group. While hematologic toxicity was 5%, febrile neutropenia was only seen in 1 patient (2.5%). Blood counts improved in 3 days with supportive treatment (Granulocyte colony-stimulating factor) (White Blood Cell: >3.500/mm^3).

Cardiovascular toxicity was never observed in this group. Neuropathy developed in only 4 patients (10%) in this group. Patients' complaints disappeared in long-term follow-up. Only one patient requested to stop the treatment due to medication side effects. None of the patients underwent dose reductions.

All the patients' pain disappeared or decreased. Analgesics were stopped in 35% of the patients, while 65% reported a reduced need for analgesics. Fatigue, weakness, and lack of appetite occurred in 5% of patients. In this group, forty-five percent of the patients complained of the difficulty of going to the hospital (Tables I-II).

DISCUSSION

Once patients are diagnosed with cancer, their treatment is planned according to the stage of the disease. Patients with localised prostate cancer are treated with hormonal therapies along with surgery or radiotherapy. In patients with locally advanced or metastatic disease, progression-free survival can be extended between 12-33 months with hormonal ablation treatment. But with the passage of time, despite hormonal treatment, the disease progresses and becomes hormone-resistant. This stage of the disease requires palliative care including chemotherapy agents along with next-generation hormone agents.

Table III: Statistical distribution of the responses.

	3-week treatment group	1-week treatment group	p-value
Survival time (mean rank)	35.56 months (min: 7, max: 78)	44.33 months (min: 14, max: 75)	0.09 (Mann Whitney U test)
Survival time (median)	32 months	41 months	
Age distribution, year (70 and over)	10 (25.6%)	33 (82.5%)	<0.001 (chi-square test)
ECOG 1 and 2	4 (10.3%)	32 (80%)	<0.001 (Fisher's exact test)
Dosage reduction (70mg/m2/day)	14 (35.9%)	0	<0.001 (Fisher's exact test)
Admission to hospital	11 (28%)	0	<0.001(Fisher's exact test)
Hematological toxicity	16 (41%)	4 (10%)	0.002 (Fisher's exact test)
Fatigue	35 (89.7%)	2 (5%)	<0.001(Fisher's exact test)
Febrile neutropenia	12 (30.8%)	1 (2.5%)	0.001(Fisher's exact test)
Going to the hospital	4 (10.3%)	18 (45%)	<0.001(Fisher's exact test)
Request to stop treatment	18 (46%)	1 (2.5%)	<0.001(Fisher's exact test)
PSA response			
50 and over	3 (7.7%)	0	
49-20	3 (7.7%)	0	
20-5	6 (15.4%)	5 (12.5%)	
5 and below	27 (69.2%)	35 (87.5%)	0.06 (Chi-square test)
PSMA-pet response			
Complete response	29 (74.4%)	25 (62.5%)	0.3 (Chi-square test)
Partial response	3 (7.7%)	6 (15%)	
Stable disease	3 (7.7%)	7 (17.5%)	
Progression	4 (10.3%)	2 (5%)	

Chemotherapy can be administered not only in the metastatic stage but also in patients with a high tumour burden or can be administered as a neoadjuvant treatment before radiotherapy. All of the studied patients had hormone-refractory disease.[18,19]

Metastases and Gleason score distributions were similar in both groups and were consistent with the literature (Table I).[18,20]

PSMA PET responses rates and PSA response were similar in both groups. There was no statistically significant difference (Table III). The results of the study were consistent with the literature.[19,20]

There are independent studies conducted in 2004. Docetaxel, used in the systemic treatment of metastatic hormone-resistant prostate cancer (mHRPC), was the first chemotherapy drug receiving FDA approval and improving survival. In the TAX 327 study, 1006 patients were divided into three groups, docetaxel (q3w) once every 3 weeks, docetaxel once a week, and mitoxantrone once a week. Every group took daily 10 mg prednisolone additionally. Docetaxel q3w significantly extended overall survival (median 18.9 months *versus* 16.5 months, p = 0.004) compared to mitoxantrone, and higher rates of PSA response (*i.e*. 50% decrease in PSA compared to onset; 45% *vs*. 32%, p <0.001), and pain control were ensured (35% *vs.* 22%, p = 0.01). Patients who received docetaxel weekly found similar responses compared to docetaxel of 3-week but had no significant benefit in their overall survival (median of 17.4 months).[21] However, older patients treated with docetaxel once every 3 weeks experienced significant toxicity including neutropenic fever, hospitalisation, diarrhoea, and dehydration. Treatment with weekly docetaxel was less myelosuppressive than the 3 weekly regimen. The weekly regimen was recommended as a suitable treatment option for elderly and frail men with mHRPC.[21]

In the Southwest Oncology Group (SWOG) 99-16 study, 770 patients received either docetaxel + prednisolone or mitoxantrone + prednisolone once every 3 weeks. Survival in patients in the docetaxel group was significantly high compared to the mitoxantrone group (17.5 *vs*. 15.6 months, p = 0.02). Following these studies, docetaxel treatment (docetaxel 75mg/m^2 once every 3 weeks + 10mg oral prednisolone per day) became standard in patients with mHRPC.[22]

The most commonly observed side effects linked to docetaxel use (in TAX 327 and SWOG, respectively) were found to be cardiovascular toxicity (10% and 47%), hematologic toxicity (32% and 53%), and neuropathy (30% and 23%).[21,22] In this study, cardiac toxicity was 5% in the 3-week group and was not observed in the weekly group. Neuropathy was observed to be 10% in both groups.

In the present study, all of the patients completed the treatment despite advanced age and poor ECOG performance. And, it was quite toxic in the 3-week regimen which is consistent with the literature. The fact that there was virtually no toxicity in the weekly regimen made us glad while increasing the comfort of patients and their relatives (Table II). Patients with older age and lower ECOG performance rates, on the other hand, were many more in this study than those found in other researches.

In this study, hematologic toxicity was 41% in the 3-week group, while febrile neutropenia was 30.8%. In the weekly regimen, hematologic toxicity was 5%, while febrile neutropenia was seen only in one patient (2.5%, Table II).

There was a high statistically significant difference between the two groups in rates of hematologic toxicity, febrile neutropenia, and fatigue in favour of the weekly regimen (p-

value: 0.002, 0.001, <0.001, respectively, Table III). Hematological toxicity and febrile neutropenia values of the weekly group in this study were lower than in other studies in the literature.[21,23]

The tendency to discontinue treatment in the 3-week regimen was very significantly high (p <0.001). The difficulty of arriving at the hospital was significantly in favour of the 3-week regimen (p = <0.001, Table III). None of the studies in the literature provided information about these side effects. As a result of these applications, it was found that patients were more compatible with chemotherapy when given a weekly regimen and no serious side effects occurred.

Overall survival was 35.56 months in the group of 3-week protocol (min:7 months, max:78 months, median: 32 months) and 44.33 months in the group of 1-week (minimum:14 months, maximum:75 months, median:41 months). This difference was not statistically significant but the slight difference is in favour of weekly regimen (p= 0.09, Table III). Other studies in the literature report that there is no statistical significance.[24,25] The average survival has been reported as a median of 19.2 months in the 3-week regimen, while in this study the median survival time of patients with a 3-week regimen was measured as 32 months.[18,20]

In another study looking at whether the myelosuppression effect of docetaxel could be reduced by alternative dose schemes, 361 patients were divided into two groups, including the standard 75mg/m^2/day (once every 3 weeks) and 50 mg/m^2/day (once every 2 weeks). The time to cessation of treatment for any reason was found to be significantly longer in the 2-weeks application. Also, grade 3-4 toxicities including neutropenia were found more frequently in the group of 3-weeks. It was noted as a result of the study that there may be an alternative treatment scheme for the patients who are likely to have myelosuppression.[23]

In the FIRSTANA study, cabazitaxel (25 mg/m^2/day to 20 mg/m^2/day group) and docetaxel (75 mg/m^2/day) were compared in patients with metastatic hormone-resistant prostate cancer at the first stage. Despite the lack of overall survival and progression-free survival difference in all the groups (25.2 months, 24.5 months, 24.3 months), grade 3-4 toxicity rates were found to be very high (60%, 41%, 46%, respectively).[26]

In the GETUG-AFU 15 study, one group of metastatic hormone-sensitive prostate cancer patients was given docetaxel 75 mg/m^2/day (once every 3-weeks) + ADT (orchiectomy or LHRH analogues) while the other group was given ADT alone. Median survival in the docetaxel group was 58.9 months, while neutropenia was 40%. Four patients died due to treatment-related complications. The ADT group alone showed no adverse effects. [15,16]

The present study was conducted on patients with hormone-resistance.

In the CHAARTED study, metastatic hormone-sensitive patients were divided into ADT and docetaxel (75 mg/m^2/day/3 weeks) + ADT groups. In the docetaxel added group, survival was 57.6 months, while in the group of ADT alone, it was 44 months. Febrile neutropenia was found as 6.2%.[17]

In the literature, 3 different studies showed docetaxel-related hematologic toxicities, fatigue, gastrointestinal (nausea, vomiting, diarrhoea) side effects, alopecia, neuropathy, and mucositis. Febrile neutropenia was detected in 12%, 8%, and 6%.[15,17,26]

The age group in this study was higher than those reported in the literature. The average age was 67.2 years in the 3-week regimen and 77.3 years in the weekly regimen. The median age was between 63 and 65 years in all the studies in the literature.[21,22,23] In this study, 40% of the patients on the weekly regimen were 81 years or older. The patients over the age of 70 years were found to be statistically significant in favor of the weekly regimen (p<0.001, Table I-III). Therefore, the cause of death of the most of the patients in this study was old age. There were some limitations in this study, the first of which was that the number of patients over the age of 70 was more in the weekly docetaxel group, and patients under the age of 70 were more in the 3-week Docetaxel group. The other limitation is that patients with ECOG performance of 1-2 were more in the weekly Docetaxel group. Patients with zero (0) ECOG performance were more in the 3-week Docetaxel group. In particular, patients over the age of 70 and with ECOG performance of 1-2 were enrolled in the weekly Docetaxel group. There were no patients with these two characteristics in the 3-week group. Again, those who were under the age of 70 and had zero ECOG performance (0), were completely enrolled in the 3-week docetaxel group. There were no patients with these two characteristics in the weekly group. The study was conducted only on patients who were admitted between January 2013 and December 2013 and followed up for 8 years. Therefore, the number of patients was few. Although a statistically significant difference was found between the two groups in the study, it would be more beneficial to conduct it with a larger patient group.

CONCLUSION

Weekly Docetaxel with oral prednisolone is an effective and well-tolerated regimen for metastatic hormone-resistant prostate cancer in the elderly and patients having poor performance status. This regimen has less toxicity as compared to the 3-week regimen of Docetaxel.

ETHICAL APPROVAL:

Ethics committee approval of Ankara Training and Research Hospital (E. Board-E-21-711) dated 29.09.2021 and No. E-93471371-514.01.02 was taken.

PATIENTS' CONSENT:
Written informed consents were obtained from all the patients.

COMPETING INTEREST:
The authors declared no competing interest.

AUTHORS' CONTRIBUTION:
MS, GC: Conceived the study design, involved in data collection, performed the statistical analysis, interpreted data, and prepared the manuscript draft. All the authors critically reviewed the final version of the manuscript and approved it for publication.

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