



AN INDIAN PROSPECTIVE STUDY OF DOCETAXEL THERAPY IN CRPC: CAN PRETREATMENT FACTORS PREDICT THE RESPONSE

Urology

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ABSTRACT

Introduction: Studies on the effects of chemotherapy in Indian Castration-Resistant Prostate Cancer (CRPC) patients are very limited and world data is inconsistent. The purpose of the present study is to assess the effects of Docetaxel therapy in CRPC in Indian patients in terms of survival benefit, both progression-free survival, and overall survival. This study also analyzes the effects of various factors on the survival of CRPC patients.

Methodology: This is a single institutional prospective observational study. CRPC patients were treated with Docetaxel and followed till death as the primary endpoint or till the end of the study. Survivals were calculated with the Kaplan Meier method. Factors affecting survival were analyzed with univariate and multivariate analysis by log-rank t-test and Cox proportion hazard regression analysis.

Result: Out of enrolled 101 patients, 78 were treated with Docetaxel. A decline in PSA (>50% reduction) was observed in 61.54%. Radiological response of regression noted in 40 % Nuclear Bone Scan and 19.23% CT/MRI by RECIST criteria. Progression-free survival and overall survival with Docetaxel (n=78) were 11.8 and 21 months respectively. Hemoglobin less than 11 gm%, Alkaline phosphatase more than 115 IU/dl, PSA more than 14 ng/ml, Gleason score more than 7 and duration from diagnosis of carcinoma prostate to CRPC less than 24 months, the number of chemotherapy cycles less than 6 were all found to be significantly associated with poor overall survival in univariate analysis while only Hemoglobin (P=0.0159) showed an independent association with overall survival in multivariate analysis.

Conclusion: Overall and progression-free survival of CRPC patients with Docetaxel is 21 & 11.8 months respectively. Hemoglobin, Alkaline phosphatase, PSA, Gleason score, Docetaxel cycle, and duration from diagnosis of carcinoma prostate to CRPC were found to be significantly associated with poor overall survival.

KEYWORDS

CRPC, Prostate Cancer, Docetaxel, Progression free survival

INTRODUCTION

After one decade of FDA approval, Docetaxel is still the treatment of choice for Castration-Resistant Prostate Cancer (CRPC). Progression-free survival & overall survival of metastatic CRPC with Docetaxel ranges from 4.3 to 11 months & 16 to 18 months respectively.^{1,2}

Carcinoma Prostate prevalence and aggressiveness, as well as genomic alterations, vary in different geographic locations. Data on the effect of chemotherapy in CRPC on Indian patients is very limited and world data is inconsistent.

The purpose of the present study is to assess the effects of Docetaxel therapy in CRPC in Indian patients in terms of survival benefit, both progression-free survival, and overall survival.

This study also analyzed the effects of factors like age, Gleason score, hemoglobin, prostate-specific antigen (PSA) at the time of CRPC, ECOG performance status, baseline alkaline phosphates, duration from diagnosis of Carcinoma prostate to Castration resistance prostate cancer, and the number of Docetaxel cycles on survival of CRPC patients.

MATERIALS AND METHODS

This is a single institutional prospective observational study. All Histological Proven Carcinoma Prostate patients, who were on Androgen deprivation therapy, and became castration-resistant between July 2007 to March 2014 were included in this study. Patients having a history of any other malignancy were excluded from the study. After recording baseline information like PSA at diagnosis of carcinoma prostate and at CRPC, treatment received for primary cancer (if any), ECOG performance status & Gleason score, all enrolled patients were followed at three weekly intervals. Docetaxel was given at three weekly intervals in doses of 75mg/m² till the disease progression or intolerance or PSA decline after 10 cycles. Pre chemotherapy and post-chemotherapy complete blood count and kidney function test at 1 week were done in every patient. Patients who refused chemotherapy were offered Fostesterol 120 mg TDS or Abiraterone 1000mg OD or only best supportive care and excluded from the study, however, they were also followed as per the protocol. Treatment regimens were continued till the progression of the disease. Docetaxel refractory patients were offered the second line Cabazitaxel or Abiraterone. PSA, Alkaline Phosphatase, complete blood count, kidney function test was done in all patients at three weekly intervals.

Radiological investigations like bone scan and MRI scan/ CT scan were done at 6-month intervals or early if required clinically. All associated complications were recorded. All cases were followed till death as the primary endpoint or till the end of the study. Survivals were calculated with Kaplan Meier survival graphs. Univariate and multivariate analyses were done by log-rank t-test and Cox proportion hazard regression analysis respectively. Ethical approval from the institutional ethics committee was taken.

RESULT

A total of 101 patients were enrolled in this study from July 2007 to March 2014, out of which 78 were treated with Docetaxel, 10 with Fostesterol and 13 patients chose not to take any treatment. All patients were offered Docetaxel but those patients who refused chemotherapy were managed by other agents. The mean age of the patient was 70.28 years, Median Gleason 7, median ECOG 1. Twelve patients had visceral and seventy-nine had bony metastasis at the time of CRPC in available records of 81 patients.

Table 1 : Patients characteristics (n=101)

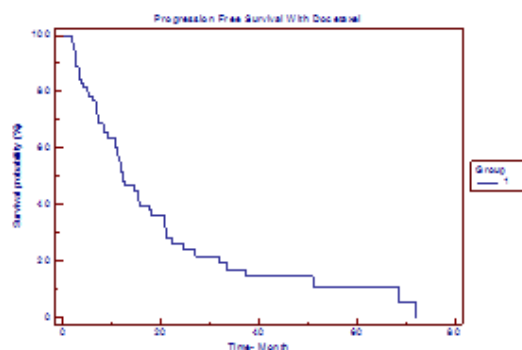
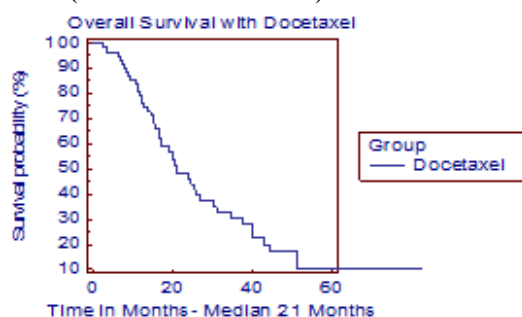
Patient	Mean	Median	Range
Age(years)	70.28	70	52-88
Gleason	7.51	7	4-10
ECOG	1.15	1	0-3
Hemoglobin (gm/dl)	11.89	11.8	8.53 to 15.3
Alkaline Phosphatase (IU/dl)	241.52	115	57 to 5392
PSA at CRPC (ng/ml)	92.06	13.83	2.64 to 1493
Duration From Ca Prostate diagnosis to CRPC (Months)	33.28	23.4	5.1 to 160.2
Visceral Disease -12/81, Bone Metastases= 79/81, Non metastatic 02/81			

Response Of treatment

A decline in PSA (>50% reduction) was observed in 61.54% with Docetaxel therapy. We compared pre and post-Docetaxel radiological scans in sixty patients and found the radiological response of regression in 40 % Nuclear Bone Scans and 19.23% RECIST (Response Evaluation Criteria In Solid Tumors) response in CT/MRI. Progression-free survival and overall survival with Docetaxel (n=78) were 11.8 and 21 months respectively, while overall survival with Fostesterol and only best supportive care group (No active treatment) was 17.36 and 12.46 months respectively.

Table 2: Survival with first-line therapy in CRPC group (n=101)

	Docetaxel (n=78)	Fosfestrol (n=10)	No treatment (n=13)	Combined (n=101)
Over All Survival (Months)	21	17.36	12.46	20.63

**Fig1: Kaplan Meier curve of progression-free survival (PFS) for Docetaxel. (Median PFS= 11.8 months) n=78****Fig 2: Kaplan Meier curve of Overall survival (OAS) with Docetaxel (n=78). (Median OAS= 21 months)****Factors Affecting Survival**

Univariate analysis of various factors affecting the survival of CRPC patients listed in table 3 was done by Kaplan Meier survival method and Log Rank P-value was calculated. Median values were taken to convert the continuous variable into the dichromatic variable.

Hemoglobin less than 11 gm%, Alkaline phosphatase more than 115 IU/dl, PSA more than 14 ng/ml, Gleason score more than 7 and duration from diagnosis of carcinoma prostate to CRPC less than 24 months, the number of chemotherapy cycles more than 6 were all found to be significantly associated with poor overall survival in univariate analysis by Log-rank p test. All other parameters including age and ECOG status were found not to be significantly associated with overall survival.

Table 3: Summary of the association between patient characteristics, median overall survival (OAS), and Log-rank p-value in univariate analysis.

Characteristics	Value	No	Median OAS	Log-rank P test	Hazard Ratio
Age	>70	39	19.86	$P=0.35$	1.31
	≤70	39	24.7		
Hemoglobin	≤11	19	15.26	$P=0.04$	0.51
	>11	59	25.63		
Alkaline Phosphatase	≤115	38	30.16	$P=0.05$	1.70
	>115	40	16.86		
Gleason sum	≤7	41	37.46	$P=0.002$	2.33
	>7	37	16.83		
ECOG	≤1	55	21.0	$P=0.72$	1.13
	>1	23	24.7		
PSA	≤14	40	24.00	$P=0.017$	1.95
	>14	38	20.36		
Docetaxel cycles (n=78)	≤6	41	15.93	$P=0.004$	0.45
	>6	37	27.0		
Duration from Ca Prostate to CRPC	≤24	41	16.86	$P=0.001$	0.41
	>24	37	37.46		

Cox proportional hazards regression analysis:

Multiple regression analysis was done for factors showing statistically significant association ($P \leq 0.05$) with overall survival i.e. PSA, Alkaline phosphatase, hemoglobin at CRPC diagnosis, duration from carcinoma prostate diagnosis to CRPC, number of Docetaxel cycles, and Gleason score of the tumor. The Multivariate analysis was done with the Cox proportional hazard regression model using Medcalc software version 12.0.0.0. When we compared all factors together only Hemoglobin ($P=0.0159$) showed an independent association with overall survival.

Table 4. Cox Proportion hazard regression analysis

Covariate	Univariate (P Value)	Multivariate (P-value)
Age	0.1061	0.0702
Hb	0.0171	0.0159
ALP	0.0334	0.4824
Gleason	0.1383	0.2264
ECOG	0.6650	0.3090
PSA	0.1496	0.8776
Cycles	0.0798	0.1179
Duration	0.2040	0.1923

DISCUSSION

Docetaxel is the gold standard therapy in the management of metastatic castration-resistant prostate cancer since 2005¹. Various therapies can be offered to patients who are not a good candidate for Docetaxel therapy, these include second-line hormonal therapies, Enzalutamide, Nilutamide, Fosfestrol, Abiraterone (CYP17 inhibitor), and other new molecules.

The progression-free survival (PFS) as reported in the TAX 327 study was 6 months². Different international studies have reported PFS with Docetaxel ranges from 4.3 months to 11 months. (Saitou et al PFS 8.8 months³, Shiota et al PFS 5.1 months⁴, Li et al PFS 8 months⁵, Kita et al PFS 5.3 months⁶, Miyake et al PFS 4.3 months⁷, Yanagihara et al PFS 7.1 months⁸, Miura et al PFS 7.5 months⁹, Petrioli et al 7.7 months¹¹, Fossa et al 11 months¹², Kelly 7.5 months¹³).

The patients who refused Docetaxel (n=23), although excluded from the study, were offered Fosfestrol (n=10). Some of these patients (n=13) chose not to take any further medication. We continued to follow up with these patients as well on a similar protocol. This allowed us to study any difference in survival if not given Docetaxel. The progression-free survival of these groups of patients could not be calculated due to inconsistent follow-up in fosfestrol (n=10) and no treatment group (n=13).

The overall survival (OAS) of Indian patients was 20.63 months including the Docetaxel group (21 months), fosfestrol group (17.36 months), and no therapy group (12.46 months).

In the TAX 327 study (multicentric randomized phase III study) OAS with Docetaxel was reported to be 18.9 months². Similarly, another large multicentric randomized phase III control study SWOG 9916 reported OAS with Docetaxel to be 17.5 months¹⁴.

There are limited numbers of Indian studies on CRPC survival. Two Indian studies by Nayyar et al and Mohanty et al reported overall survival as 15.1 and 22 months respectively^{15,16}.

In a large number of studies from Japan OAS with first-line Docetaxel, therapy ranges from 15.3 months to 26.4 months.

Saitou et al⁴ OAS 24.1 months, Shiota et al⁵ OAS 20.8 months, Li et al⁶ OAS 17 months, Kita et al⁷ OAS 26.4 months, Miyake et al⁸ OAS 25.4 months, Yanagihara et al⁹ OAS 20.3 months, Miura et al¹⁰ OAS 15.3 months.

Another Study from Hong Kong China by Cheung et al¹⁷ has shown median OAS as 12.2 months. Lee et al¹⁸ from Korea has reported OAS to be 22.8 months.

Some studies from the European continent by Petrioli et al¹¹, Fossa et al¹², Kelly et al¹³, Hirst et al¹⁹ reported OAS as 27.3 months, 27 months 21.5 months, and 13.5 months respectively.

Thus the overall survival time varies even in the same geographical region, which suggests that it depends upon various factors like

patients and disease characteristics at the time of diagnosis of CRPC and the extent of best supportive care provided to the patients.

The hazard ratio in our study between the Docetaxel group ($n=78$) and patients who chose no therapy ($n=13$) is 2.05 (Confidence interval 0.76 to 5.54 $p=0.001$) which is statistically significant. This reflects that survival time increases more than double in the Docetaxel treatment group, although grouping was not done by proper randomization method because Docetaxel was offered to all of them, 13 patients themselves selected no treatment at CRPC diagnosis.

Another study by Jatinder et al from Germany has reported OAS with Docetaxel and no treatment group was 21.3 and 17.3 months respectively (significant Log-rank $P=0.004$)²⁰.

These prognostic outcomes of survival in our study were similar to those in previous clinical studies of Asian populations. Overall, these findings indicate that the oncologic outcomes and benefits of Docetaxel chemotherapy among Indian men are similar to those among Asian and international patients.

In our study PSA response of more than 50% decline has been reported in 61.54% (48/78) patients with the Docetaxel group. Shiota et al⁴, Li et al⁸, Miyake et al⁶, Yanagihara et al⁹, Miura et al¹⁰, Fosså et al¹², have reported PSA decline as 44.3%, 47.4%, 55.6%, 68.8%, 67.3%, 54% respectively with first-line Docetaxel therapy. COU-302 study reported 62% PSA response with First-line Docetaxel²¹.

Radiological response by RECIST criteria in our study was 19.23% (10/52) and Nuclear Bone scan response of 40% (22/55) with Docetaxel.

Li et al⁶ have reported 21.1 % RECIST response with Docetaxel first line, while Petrylak et al¹⁴ reported 57% response.

In men with asymptomatic or minimally symptomatic metastatic CRPC, Abiraterone is an attractive first-line option given its ease of administration and relatively low toxicity profile. Similarly, the combination of Abiraterone and Enzalutamide would likely be a well-tolerated regimen in this setting and is currently under clinical investigation.

In India Abiraterone has been available only from mid-2013, after which it has been used for the treatment of CRPC, so we have very few patients in this group. To compare the Abiraterone group with other studies, we need more patient data which is likely to be available in the future.

Patients with high Gleason scores, poor response to initial androgen deprivation therapy, rapidly progressive disease, or poorly controlled symptoms may derive greater benefit from immediate chemotherapy, while a trial of Abiraterone may be reasonable in patients with less extensive or more slowly progressing disease²².

In the present study, we identified prognostic factors using mainly pre-therapeutic variables, which are easily measured by standard assays in most institutions. This facilitates the oncologist's ability to predict the survival outcomes for metastatic CRPC patients before the initiation of therapy, they may guide us to choose more aggressive treatment like cytotoxic chemotherapy for poor prognostic and high disease burden group, while poor performance status patients and low disease burden group can be managed with Abiraterone or second-line hormone therapies.

In the present study, univariate analysis by Log-rank P test have shown a significant association of median OAS with hemoglobin less than 11 gm/dl, alkaline phosphatase more than 115 IU/dl, Gleason grade of tumor more than 7, PSA at the time of CRPC more than 14, Docetaxel cycles less than 6, and duration from carcinoma prostate diagnosis to CRPC less than 24 months, while age more than 65 and ECOG performance status were not significantly associated with OAS.

In multivariate Cox proportional regression analysis out of all variables, only hemoglobin was independently associated with median OAS.

Yuan et al²³ in their study reported hemoglobin, PSA, ECOG status, alkaline phosphatase, and duration of castration resistance were

significantly associated with survival in univariate analysis but in multivariate analysis only hemoglobin, more number of Docetaxel cycle and duration to castration resistance had an independent effect on median OAS.

TAX 327 study data was analyzed by Armstrong et al²⁴ and reported a significant association of hemoglobin, alkaline phosphatase, duration of castration resistance, and more than 10 Docetaxel cycles with survival in univariate analysis. The same study with multivariate analysis proved a significant association of alkaline phosphatase and more than 10 Docetaxel cycles with median overall survival. They have taken criteria of 10 cycles of Docetaxel, while in our study we grouped our patients based on more than 6 cycles because median numbers of 6 cycles were given to our study population.

Another study from Germany by Jatinder et al²⁰ reported hemoglobin, alkaline phosphatase, PSA at CRPC, ECOG status, and duration of castration resistance had a significant individual effect in univariate analysis, while ECOG did not show independent effect in multivariate analysis. Rest all hemoglobin, alkaline phosphatase, PSA, castration resistance duration had shown significant association in multivariate analysis as well.

A recent study (May 2014) by Shiota et al⁴ from Japan, had reported ECOG, castration duration, alkaline phosphatase to have a univariate association, while alkaline phosphatase and ECOG to have a multivariate association with median overall survival. Shiota et al have taken alkaline phosphatase level of 328 IU/dl to divide the study population into two groups for comparative regression analysis, while in our study we have selected alkaline phosphatase level of 115 IU/dl as dividing value because it was the median of our study population.

This reflects that patients can be risk-stratified according to Gleason score, number of Docetaxel cycle, hemoglobin level, PSA, Duration from carcinoma prostate diagnosis to CRPC, and alkaline phosphatase. Limitations of our study included a small number of cases, nonrandomized observational study, and influence of second-line chemotherapy like cabazitaxel and other medication on survival of Docetaxel treated patients.

CONCLUSION

Overall survival data in our study population with Docetaxel (21 Months) is similar to that published in other Indian, Asian as well as international studies.

Hemoglobin less than 11 gm%, Alkaline phosphatase more than 115 IU/dl, PSA more than 14 ng/ml, Gleason score more than 7, Docetaxel cycle less than 6, and duration from diagnosis of carcinoma prostate to CRPC less than 24 months were found to be significantly associated with poor overall survival on univariate analysis. Hemoglobin was found to be significantly associated with poor overall survival on multivariate analysis.

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