Does Ethnicity Influence Response To Docetaxel Based-Chemotherapy For Patients With Castration Resistant Prostate Cancer? The New Mexico Perspective.

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Citation

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Abstract

INTRODUCTION: Metastatic prostate cancer is lethal in 15 % of the patients. Ethnic variations in response to docetaxel in patients with metastatic prostate cancer have not been studied. The aim of this study was to identify ethnic differences in the response to docetaxel, among patients with castration resistant metastatic prostate cancer.PATIENTS AND METHODS: We queried the New Mexico Cancer Registry then the electronic charts of all castration resistant metastatic prostate cancer patients who were treated with docetaxel between 1999 and 2010 at the University of New Mexico Cancer Center. Patient characteristics that might influence the response to docetaxel such as age, prior treatment including hormones, chemotherapy, radiotherapy, and surgery, concurrent chemotherapy, site of disease, baseline PSA, and number of docetaxel courses were recorded. Progression of disease after start of treatment was defined as identification of new lesions or a biochemical recurrence. The primary end point was overall survival. Secondary end points were progression-free survival and PSA response to docetaxel. RESULTS: Despite a lower incidence of prostate cancer in NM, the death rate is higher than the national average. Although not statistically significant, the overall survival for patients treated with docetaxel is highest among Non Hispanic Whites, followed by Native Americans and worst among the Hispanic population. The progression free survival was greatest in the Native American population followed by Non Hispanic Whites, followed by Hispanics. Compared to published data, the survival of New Mexicans with prostate cancer treated with docetaxel is worse.CONCLUSION: Hispanic males with castration resistant metastatic prostate cancer on docetaxel, tended to have the lowest overall survival and progression free survival, but overall the differences between New Mexican ethnicities were not statistically significant.

INTRODUCTION

Metastatic prostate cancer is lethal in 15% of the patients, and is the second most common cancer among men of all ethnicities in the United States. Castration resistant prostate cancer (CRPC) is defined as progressive prostate cancer in spite of serum levels of androgens lower than 50 ng/mL. Progression of disease manifests by prostate specific antigen (PSA) elevations and bone metastases in 90% of cases, severe pain in 35 %, and soft tissue or lymph node metastases in 20%. Docetaxel, a semi-synthetic taxane analog, is the standard of care in CRPC and exerts its effect by microtubule assembly paralysis leading to caspase induced cell death. Docetaxel is the first chemotherapeutic agent that decreases tumor burden and prolongs the survival of patients with metastatic CRPC. Among patients who initially respond to first line docetaxel, a later reintroduction produces PSA response in 48 % of patients and a median survival of 16 months after the reintroduction[2]. In the TAX-327 study (Table 1), the 48% PSA response was accompanied with pain relief and improvement in quality of life. Unfortunately, resistance to docetaxel develops rapidly, probably due to underlying genetic interactions and/or clonal selection, which could vary with ethnicity.

Figure 1

Table 1. Studies of Docetaxel in Prostate Cancer

Study	No Patients	Docetaxel Arm(s)	Control Arm	OS (months)	PFS (months)	PSA Response rate (%)
TAX 327[7]	1006	D+P D1(weekly) D3 (3 weekly)	M+P	19.2/17.8 and 16.3	NA	48/45 and 32
SWOG 9916[9]	634	D 60-70 mg/m^2 + E 280 mg TID	M+P	D+E=17.5 M+P=15.6	D+E=6.3 M+P=3.2	50/27
Univ. of Florence[11]	38	D 30 mg/m^2 Epi 30 mg/m^2	None	NA	7.4	68.4
Japanese[12]	55	D 70 mg/m^2 Prednisone	E	15.3	7.5	67.3
Canadian urology Oncology [10]	30	D 75 mg/m^2	P 5mg bid	15	5	57
Phase II Study Germany[13]	62	D 70 mg/m^2	E	24	14	61.3
Phase II Study France[14]	130	D+E (2 schedules)	M	D+E=18.6/18.4 M= 13.4	D+E =8.8/9.3 M=1.7	64
Randomized study, Belgium[15]	44-D 45-D+E	D+E	D 70 mg/m^2	D=21 D+E=19.3	D=7.3 D+E = 6.9	D=25 D+E=41

OS, overall survival; PFS, progression-free survival; PSA, prostate specific antigen; D, docetaxel; E, estramustine; M, mitoxantrone; P, prednisone; Epi, Epirubicin.

Although the African American (AA) population diagnosed with prostate cancer has a worse outcome, the situation is very different in New Mexico (NM), a multicultural state, where 43.6% and 9% of the population are Hispanic (H) (12.9% of the US population) and Native American (NA) (0.9% of the US population) with the remainder being essentially Non Hispanic Whites (NHW). Therefore, the goal of this study was to assess the efficacy of docetaxel specifically in these three ethnic groups.

PATIENTS AND METHODS

After Institutional Review Board approval, the medical records of patients with CRPC treated with docetaxel between 2000 and 2010 were queried at the University of New Mexico Cancer Center (the County Hospital) to identify differences in outcome, if any, between Hispanics, Whites, and Native Americans. Fifty records were available. The primary end point was overall survival (OS). Secondary endpoints were progression free survival (PFS) and the PSA response to treatment. OS was measured from the first treatment of docetaxel to death. PFS was defined as the duration of time on docetaxel before either a new metastatic lesion was identified or PSA progression occurred. Response to docetaxel was based on the PSA response defined by the Prostate Cancer Clinical Trials Working Group (PCGW2, 2007). PCGW2 guideline recommends measuring PSA at 12 weeks and maximum PSA percent change from baseline using waterfall plots to record the changes. PSA progression is the point at which there is a greater than 25 % increase in PSA or a greater than or equal to 2 ng/ml rise above the nadir which is confirmed by a second value 3 weeks later [3]. RECIST (Response Evaluation Criteria in Solid Tumors) version 1.1 criteria were used for identifying radiographically measurable lesions [4]. Collected patient characteristics included race, age, prior treatments, site of disease, and Gleason score at diagnosis. Treatment outcome variables were concurrent chemotherapy, baseline and nadir counts of granulocytes after chemotherapy, number of docetaxel courses, and addition of other treatments to docetaxel. Subjective indicators of disease progression such as pain were not used in this chart review.

Patient characteristics were summarized by descriptive statistics. The effect of ethnicity on continuous variables was examined by F-test of Analysis of Variance. For categorical variables, Fisher's exact test has been used to investigate the effect of ethnicity. The OS and PFS were determined by Kaplan-Meier product-limit estimates. Survival differences among ethnicity groups were tested using log-rank test for both OS and PFS. Similarly, statistical significant differences among categorical demographic variables were examined by log-rank tests. For continuous covariates such as PSA, Cox proportional hazards regression models were employed to identify statistically significant variables affecting OS or PFS. The Wald test has been used to identify significant variables along with hazard ratio and its 95% confidence interval.

The New Mexico Registry, a subset of the Surveillance Epidemiology End Results (SEER) Database, was also queried for general statistics on prostate cancer.

RESULTS

Fifty-one patients with CRPC treated with docetaxel were included in the study. Patient characteristics are described in table 2.

Figure 2

Table 2. Patient Characteristics

Characteristics	NHW N=29 (58 %)	H N=15 (30 %)	NA N=5 (10 %)	P Value
Mean age (year, range)	71.9 (52-83)	67.7 (48-82)	78.6 (74-84)	NS
Insurance Yes No	 77.8 % 22.2 %	 36.4% 63.6%	 25% 75%	0.02
Gleason score[1] <7 7 8 9	 21.8% 52.2 % 13 % 13 %	 8.3% 25% 16.7% 50%	 33.3% 0% 33.3% 33.3%	NS
Baseline PSA (mean, range)	203.82 (0.1-907.0)	530 (2-4400)	491.66 (5.1-1090.0)	0.033
Radiotherapy (%)	20.7	26.7	20	NS
Hormonal Therapy (%)	100	100	100	NS
Prior Chemotherapy (%)	3.4	6.7	0	NS

NHW, Non Hispanic White; H, Hispanic; NA, Native American; PSA, prostate specific antigen.

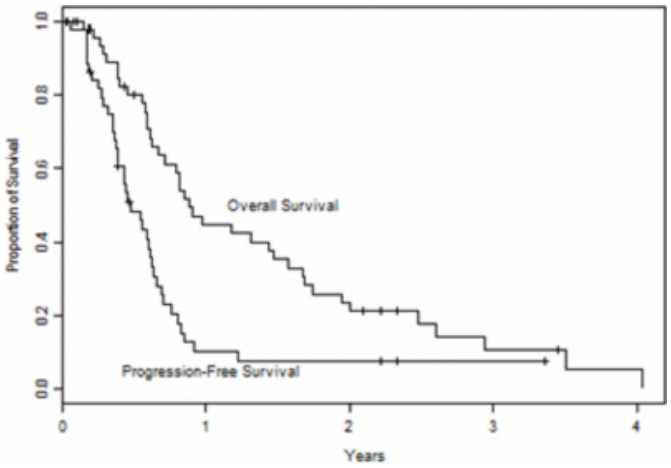
All patients were treated with prior hormonal therapy, mostly with leuprolide and bicalutamide. Median age was

71.1 years. There were 29 NHW, 15 H, 5 NA, and 1 each Asian and unknown. Twenty-two percent of the patients were on a weekly regimen at 30-35 mg/m^2 and 78 % on an every 3 week administration at doses of 60-75 mg/m^2. Concurrent chemotherapies were carboplatin (13.64 %), estramustine (68.18 %), thalidomide (4.55 %) and goserelin (4.55 %). All study patients tolerated the first cycle of chemotherapy well and did not require granulocyte stimulating factor to treat myelosuppression. The OS and PFS are shown in figure 1.

When examining the whole cohort, variables correlating with OS included PSA values at all time points, dose of docetaxel, neutrophil count after first dose of chemotherapy and the number of docetaxel courses.

Figure 3

Figure 1. Overall Survival and Progression-Free Survival after Initiation of Docetaxel Treatment



Patient characteristics of baseline PSA (p=0.0337), 12 week PSA ($p < 0.0001$) (Figure 2), PSA nadir ($p < 0.0001$) were statistically significant for OS. Similarly, patient characteristics such as baseline PSA (p value=0.0037), nadir PSA (p=0.0003), 12 week PSA (p=0.0015) were significantly associated with PFS. Hazard ratio estimates showed that the higher these variables the lower the probability of OS and PFS. A higher neutrophil count after first dose of docetaxel was associated with PSA progression (p=0.0287). Patients on the every three week administration of docetaxel had a better survival (p=0.0289) which correlated with a higher dose of docetaxel.

Figure 4

Figure 2. Waterfall Plot for PSA Changes at 12 weeks from Baseline (2a) and at Nadir from Baseline (2b)

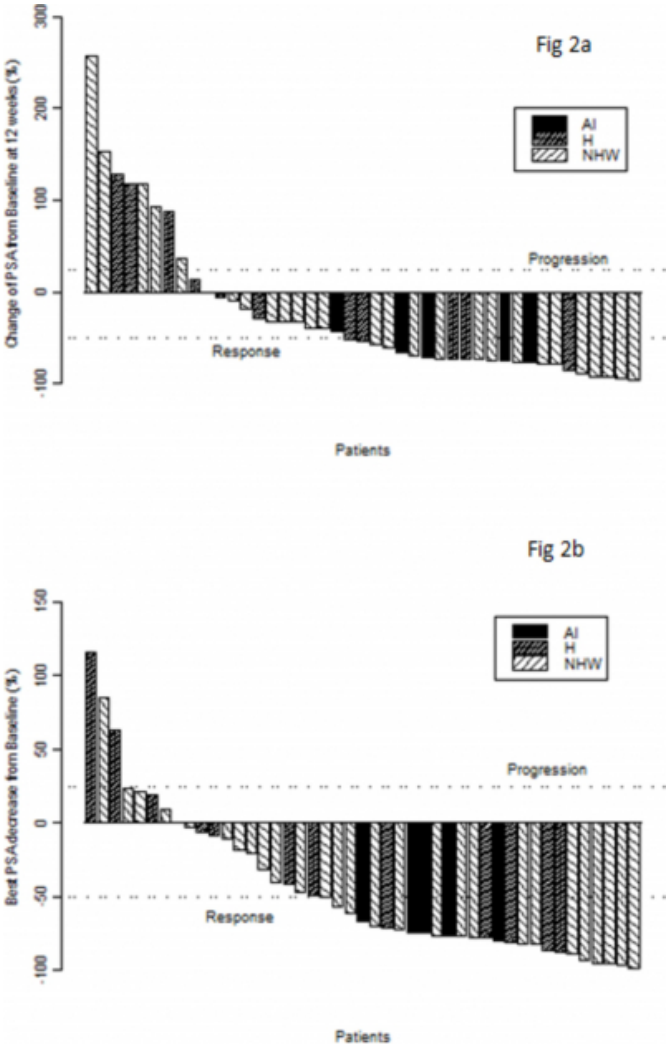


Table 3 shows the studied variables and their influence on patient outcome by ethnicity.

Figure 5

Table 3: Docetaxel Outcome Variables

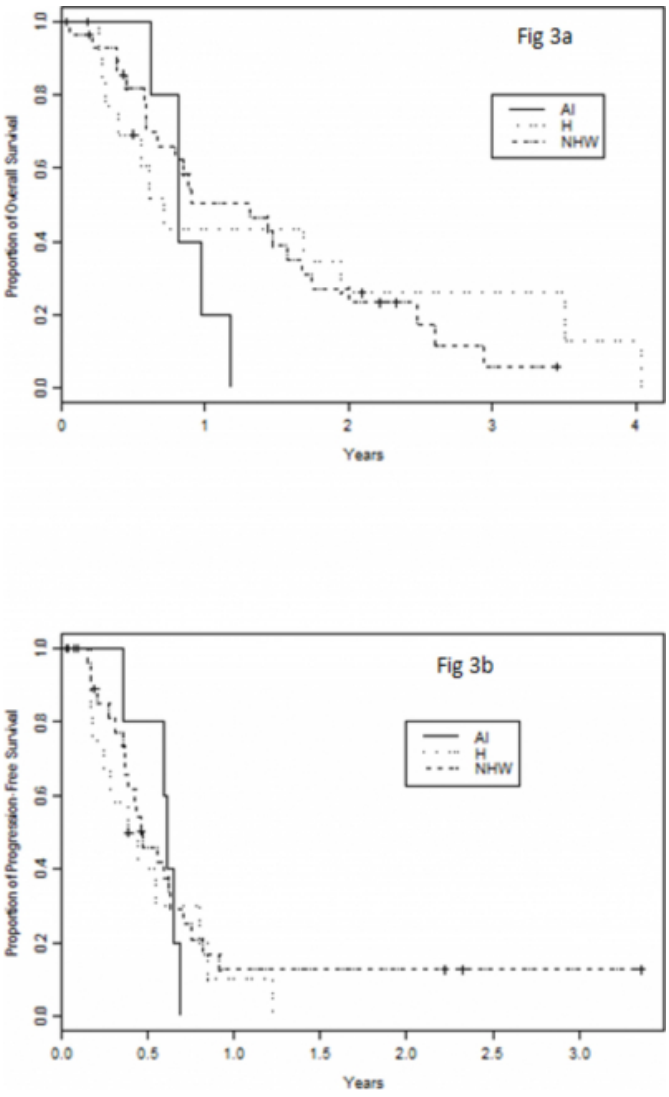
Variable	NHW	H	NA	P-value
Overall Survival (week)	68.4	37.3	42.4	NS
Progression Free Survival (week)	19.9	15.6	25.1	NS
Time to PSA progression	24.6	21.4	31.9	NS
PSA Progression				
Yes	75.9%	73.3%	100%	NS
No	22.1%	26.7%		
Maximum PSA decrease on Docetaxel (mean)	54%	81%	76%	NS
Docetaxel Dose				
Weekly	34.5%			NS
Every 3 week	65.5%	100%	100%	
Docetaxel median number of courses	4 (1-12)	5 (1-9)	4 (3-9)	NS
Toxicity after first course of chemotherapy	None	None	None	NS
Neutrophil count after first chemotherapy	5700 (0-14,600)	3860 (700-11000)	6,000 (2160-8268)	NS
New lesions while on Docetaxel				
Yes	73.5%	80%	80%	NS
No	26.5%	20%	20%	
Site of Metastatic disease (%)				
Bone	39.47	21.05	5.26	
Lymph Node	15.78	10.49	2.6	
Brain	0	0	0	0.0018
Adrenal	2.63	2.63	0	
Liver	2.63	0	0	

NHW, Non Hispanic White; H, Hispanic; NA, Native American; PSA, prostate specific antigen.

The median OS was highest among NHW (46.3 weeks), followed by NA (42.4 weeks) and worst for H (37.3 weeks) (Figure 3). However, these results were not statistically significant (p=0.54). PFS was greatest for NA (25.2 weeks), followed by NHW (19.9 weeks) and then H (15.6 weeks) (again, not statistically significant (p=0.7745). There were no differences in outcome between ethnicities.

Figure 6

Figure 3. Overall Survival (3a) and Progression-Free Survival (3b) by Ethnicity



Interestingly, H and NA were all treated with every 3 week docetaxel, now known to be better than the weekly dosing, but their survival is worse, despite a better PFS and a greater decrease of PSA values[7].

DISCUSSION

Survival of CRPC patients treated with docetaxel in this NM cohort was associated with higher doses, number of courses, and lower PSA (at baseline, nadir and 12 weeks). These are all intuitive correlations. However, age, Gleason score at diagnosis, and ethnicities in this NM cohort of patients (NA, NHW, H) did not affect survival.

The annual incidence rate of prostate cancer in New Mexico during the period of 2003 through 2007 is 143.3 as compared to the national incidence of 153.5. The annual

death rate due to prostate cancer per 100,000 deaths in New Mexico during the time period from 2003 to 2007 is 25.4 which is slightly higher than the national average of 24.7. The percentage of newly diagnosed cases of prostate cancer in New Mexico for NHW, H, NA and AA populations are 31.8 %, 31.3 %, 26.6 % and 34.3 % respectively. The percentage of all deaths due to prostate cancer in New Mexico among NHW, H, NA, and AA are 12.1 %, 11.7 %, 12.7 % and 13.7 % respectively. These numbers also show similar outcomes between NHW, H and NA. AA patients were not included in our retrospective chart review because this population makes < 2% of the New Mexican population. AA populations have been found to have a higher mortality from prostate cancer, higher incidence of prostate cancer, and more advanced disease at presentation compared to other races [1]. Such differences have not been established for H and NA. The life time probability of developing prostate cancer for the AA population is 18.25 % versus 15.25 % for the NHW and the lifetime probability of dying from prostate cancer is 4.43 % versus 2.65 % for the NHW. Ethnic differences in genotype for the genes associated with androgen metabolism – SRD5A2 and CYP3A4 may contribute to these differences [5] Patients of African descent have a higher frequency of these alleles. The better outcome seen in NHW compared to AA may be due to social factors such as education, income, and insurance status, which may all contribute to greater mortality [6].

TAX 327 study, a randomized phase III trial across 24 countries, enrolled 1006 patients. The best arm for OS, tumor response rate, pain decrease, and quality of life was the 3 weekly docetaxel regimen compared to weekly docetaxel or Mitoxantrone [7]. SWOG 9916, a randomized phase III study of 634 men with CRPC, found a 20% improvement of overall response with the combination of docetaxel and estramustine, compared to the combination of mitoxantrone and prednisone [8, 9]. The median survival of these patients was 1.5 years (95 % CI 1.4-1.7 years). A Canadian study with the 3 weekly docetaxel as second line therapy for patients who had progressed on mitoxantrone and prednisone noted a 57 % PSA response [10]. Results of several phase II studies are summarized in table 1. The NM cohort of patients has a lower OS and PFS than the ones reported with docetaxel in the literature. This may be due to the fact that most of these patients were not enrolled in a clinical trial, did not have any insurance, represented an indigent population, or presented later in the course of the disease. Other factors such as patient compliance could not be studied in this retrospective chart review.

In conclusions, there are no confirmed differences in outcome by ethnicities for patients with CRPC in New Mexico. As expected, patients who survived longer had better PSA values and more doses of chemotherapy, because their tumors were more sensitive to chemotherapy.

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