Running head: Time to castration resistance and survival

The effect of time to castration resistance on overall survival and success of docetaxel treatment in castration resistant prostate cancer patients

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ABSTRACT

Introduction: To investigate the prognostic role of time to castration resistance(TTCR) in patients who have received solely Docetaxel chemotherapy regimen(DCR) for castration resistant prostate cancer(CRPC).

Methods: Between Jan 2004 and Dec 2015, data of 162 patients who have received DCR for CRPC are detected. Patients were divided into three groups according to TTCR: Group 1(≤12 months), group 2(13-24 months), and group 3(>24 months). Data of age, clinical stage, Gleason grade(GG), previous treatments, site of metastases, Prostate-specific antigen (PSA) values, TTCR, overall survival, biochemical progression free survival(PFS) and PSA response to docetaxel were recorded.

Result: The mean age of the 162 patients was 74.4±8.5. Data on mean age, type of castration, adding estramustine to docetaxel, secondary hormonal manipulation, Gleason grade, clinical T stage at initial diagnosis and site of metastases were comparable between three groups. All PSA values were statistically significant higher in group 1 than other groups. PSA response to docetaxel was 59.2% in all patient and it was worse in group 1 than other groups(*P*=.009). Two years OS rates were 7.6%, 25% and 32.3% in group 1, 2 and 3, respectively. Median survival rates were 7, 14 and 23 months in group 1, 2 and 3, respectively, and this difference was statistically significant (*P*=.016). On multivariate analysis, TTCR was found to be independent prognostic factor for overall survival and response to docetaxel treatment.

Conclusion: TTCR appears to be an independent prognostic factor for patients who are candidates for DCR.

INTRODUCTION

Androgen deprivation therapy (ADT) is the main treatment option for metastatic prostate cancer.[1] After an initial response, resistance to ADT occurs in most patients, with the result that the median survival among patients with metastatic prostate cancer is approximately 3 years.[2] Eventually most of the patients will progress to castration resistant prostate cancer (CRPC). Previously Docetaxel chemotherapy regimen (DCR) was the mainstay treatment for CRPC patients.[3] The therapeutic armamentarium for metastatic castrationresistant prostate cancer (CRPC) has rapidly expanded in recent years. Recently new agents with diverse mechanisms of action (sipuleucel-T, abiraterone acetate, enzalutamide and radium-223) were shown to prolongoverall survival.[4-7] Although abiraterone and enzalutamide are widely used, cytotoxics continue to play an important role in the management of metastatic CRPC. The best timing for the use of cytotoxic chemotherapy remains questionable and varies among patients. In patients with disease progression and who are symptomatic or harbour visceral metastases, cytotoxic chemo-therapy may have a role to play earlier in the disease course.

Due to emerging treatment options for CRPC, it is important to define predictive markers to categorise patients suitable for DCR and prevent the ineffectiveness, costs and side effects of this treatment. Time to castration resistance (TTCR) was defined as a predictive factor for secondary endocrine treatment and mixed chemotherapy regimens in previous studies.[8,9] We aimed to investigate the prognostic role of TTCR in patients who have received solely DCR for CRPC.

MATERIALS AND METHODS

In this retrospective study we have evaluated our metastatic prostate cancer database. Between Jan 2004 and Dec 2015, a total of 211 patients who have received DCR for CRPC aredetected. Since the study was retrospective, no ethical problems were encountered. To prevent the flare up phenomenon, antiandrogen was started 10 days before LHRH agonist started and then patients received only LHRH agonist therapy. PSA and testosterone levels were measured once every 3 months during ADT therapy. CRPC was defined as biochemical or radiological disease progression on ADT with castrate testosterone levels (< 50 ng/dL). Biochemical progression was defined as a 50% increase in two of three consecutive PSA measurements taken at 1 week intervals, provided that the PSA value was > 2 ng/mL. Forty nine patients were excluded from the study due to; indeterminate starting dates for primary ADT or chemotherapy (n=24), discontinuation of chemotherapy due to patient incompliance or preference (n=11), significant lack of follow-up data (n=10) and multiple cancer diagnosis (n=4). Therefore, the remaining 162 patients were eligible for the final analysis. Clinical T stage at initial diagnosis was evaluated in the patients and is shown in table 2.

Docetaxel was administered I.V. at the standard dose of 75 mg/m^2 every 3 weeks as a 1-h infusion with dexamethasone prophylaxis and oral prednisolone 5 mg twice daily as described previously.[3] Prostate specific antigen (PSA) response rates were measured using Prostate Cancer Working Group (PCWG) 2 criteria.[9] As recommended by the PCWG 2, PSA response was defined as 50% declines from baseline and a 25% increase confirmed with a second PSA reading a minimum of 3 weeks later was used to determine PSA progression and response duration. Blood tests, including PSA, were measured every

three weeks, and radiological assessments, including computed tomography scans of the thorax, abdomen and pelvis and bone scans, were carried out after PSA progression were detected. Follow-up data, including time to biochemical progression and date of death, were available for all patients. Time to castration resistance (TTCR) was calculated from the time of ADT initiation irrespective of stage until confirmation of CRPC.

Data on patient and characteristics, were collected from a retrospective review of medical records. The following variable were recorded for analysis; age, stage, Gleason grade(GG), previous treatments, site of metastases, PSA value and TTCR. Biochemical progression and death due to any reason were considered as events. Kaplan Meier analysis were performed to obtain estimates for overall survival (OS) (Figure 1). Cox regression analysis was performed to define independent prognostic factors. Variables that were significant in univariate analysis or close to p value 0,05 although not statistically significant, were included in the cox regression analysis. P value < 0,05 was accepted the statistical significance criteria. SPSS 17.0 was used for the analysis.

RESULTS

The mean age of the 162 patients was 74.4±8.5. Patient characteristics are listed in table 1. Thirty men (18.5 %) had received prior local therapy for prostate cancer with curative intent. Of these 30 men, 20 and 10 had received radical prostatectomy and radiotherapy, respectively. Median nadir PSA value during ADT, median PSA value immediately before docetaxel, median nadir PSA value during docetaxel, median highest PSA value after starting docetaxel were 3.2 (range: 0.008-150), 78.7 (range: 1.5- 1092), 38.4 (0.03-400), 113.3 (range: 3.2-617), respectively. Median survival (minimum survival was 3 months and maximum survival 39 months. When this data is ranked from lowest to highest, the

median value in the middle is the median value, which is calculated 15) and 2 years survival rate were 15 month and 18.5%, respectively. PSA response to docetaxel was 59.2%.

Patients were divided into three groups according to TTCR: Group 1(≤12 months), group 2(13-24 months), and group 3(>24 months). Data on patient and disease characteristics of three groups were compared. Data on mean age, type of castration, adding estramustine to docetaxel, secondary hormonal manipulation, Gleason grade,clinical T stage at initial diagnosis and site of metastases were comparable between three groups (Table 1). Median nadir PSA value during ADT(*P*=.014), median PSA value immediately before docetaxel(*P* =.024), median nadir PSA value during docetaxel(*P*=.026), and median highest PSA value after starting docetaxel(*P* =.037) were statistically significant higher in group 1 than other groups. Median survival rates were 7, 14 and 23 months in group 1, 2 and 3, respectively, and this difference was statistically significant(*P*=.016). PSA response to docetaxel treatment were worse in group 1 than other groups(*P*=.009). Median biochemical PFS rates were 3, 6, and 10 months in group 1, 2 and 3 respectively, and this difference was statistically significant(*P* =.04). There was no statistically significant difference between the 3 groups in terms of the median follow-up time (Table 1). All comparisons were detailed in table 2. Two years OS rates were 7.6%, 25% and 32.3% in group 1, 2 and 3, respectively (Table 1) and in the Kaplan Meier analysis found overall survival in group 1 was statistically significant worse than group 2 and group 3 (Figure 1).

On multivariate analysis, TTCR was found to be independent prognostic factor for overall survival (95% CI: 1.924-3.282, HR = 2.8 *P*=.001,) and response to docetaxel treatment (95% CI: 1.156-4.086, HR= 1.9, *P*=.001) (Table 2).

DISCUSSION

DCR was established as the standard care in CRPC after the outcomes of two randomized studies.[3,10] The results of these two phase III studies showed that docetaxel in a 3-weekly regimen improved OS, which was the primary endpoint of both trials. Additionally, DCR offered better palliation and quality of life.However, the side effects of chemotherapy and the relatively elder CRPC population was the basis for tailoring the therapy. A nomogram was formed using independent prognostic factors in TAX 327 study to simplify important clinical decisions such as when to start cytotoxic chemotherapy. These prognostic factors were presence of liver metastases, number of metastatic sites, clinically significant pain, Karnofsky performance status, type of progression, pretreatment PSA doubling time, baseline PSA, tumor grade, baseline alkaline phosphatase, and baseline hemoglobin.[11] Furthermore, in the TAX 327 secondary analysis study, four independent risk factors were defined, risk groups were developed and validated for predicting PSA decline and OS in men with mCRPC. These independent risk factors are pain, visceral metastases, anaemia, and bone scan progression.[12] The approval of abiraterone and enzalutamide in pre-Docetaxel setting enhanced the need for the identification of patients who may have greater benefit by the use of chemotherapy. High Gleason score at the time of diagnosis and patients who had a short response to prior ADT (<16 months) had poor PSA responses when treated with secondary hormonal therapies such as abiraterone and enzalutamide.[13,14] Loriot et al .evaluated median duration of response to initial ADT in patients treated with androgen receptor axis targeted drugs. In this study patients who had longer initial ADT response demonstrated better responses for secondary treatments and 12 months was the cut-off.[9] Bellmunt et al. examined COU-AA-301 and COU-AA-302

patients and demonstrated the positive effects of longer exposure to prior ADT on survival.[15] However, the clinical benefit of abiraterone was maintained in all groups. Zheng et al. evaluated the prognostic effects of circulating tumor cells (CTC). In this meta-analysis demonstrated that CTC positivity indicates poor prognosis in patients with CRPC and can be used as an independent prognostic factor of survival rate in patients with CRPC.[16] Also a case of penic metastasis in a 70-year-old geriatric male patient with prostatic adenocarcinoma is reported. who was treated with cabazitaxel chemotherapy beyond 20 cycles with a good response and acceptable minimal toxicity.[17]

In an era of shifting paradigms in CRPC with multiple options becoming available prior to DCR, prior response to ADT may serve to discriminate between patients who benefit most from docetaxel chemotherapy as first-line treatment. The cell cycle is important because many chemotherapy drugs work only on cells that are actively reproducing. Docetaxel is a mitotic inhibitor and based on this information we expected better responses in shorter TTCR. However,in our study shorter TTCR was associated with lower PSA response and survival. Particularly in patients who have TTCR < 12 months demonstrated the worse prognosis. Shorter TTCR is also associated with short doubling time and fast cell cycle, which is also a poor prognostic parameter.[18] The outcomes of this study confirm the previous study published by Bournakis et al.[8] In a series which have included docetaxel and non-docetaxel regimens, they have demonstrated < 2 year of TTCR as an independent prognostic factor for PFS and OS. According to these results we can accept TTCR as a prognostic factor, without relating to any therapy. The processfor the secondary therapy must concern quality of life and side effects of the therapy. This study has several limitations. In this retrospective study we did not have adequate data

to evaluate radiological PFS and pain scores. Although all of the patients were treated with DCR, a significant number of patients received estramustin in their regimen which causes some heterogeneity. Due to the health insurance restriction, none of our patients were treated in pre-DCR setting with novel drugs such as abiraterone acetate and enzalutamide. Only the minority of the patients received abiraterone acetate after the development of unresponsiveness of chemotherapy.

CONCLUSIONS

TTCR appears to be an independent prognostic factor for patients who are candidates for DCR. Although utilizing chemotherapy instead of secondary hormonal treatments seem to be reasonable in patients who have developed early castration resistance , the patients must be informed of the lower response rates for chemotherapy.

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CONFLICT OF INTEREST

The authors have declared no conflict of interest.

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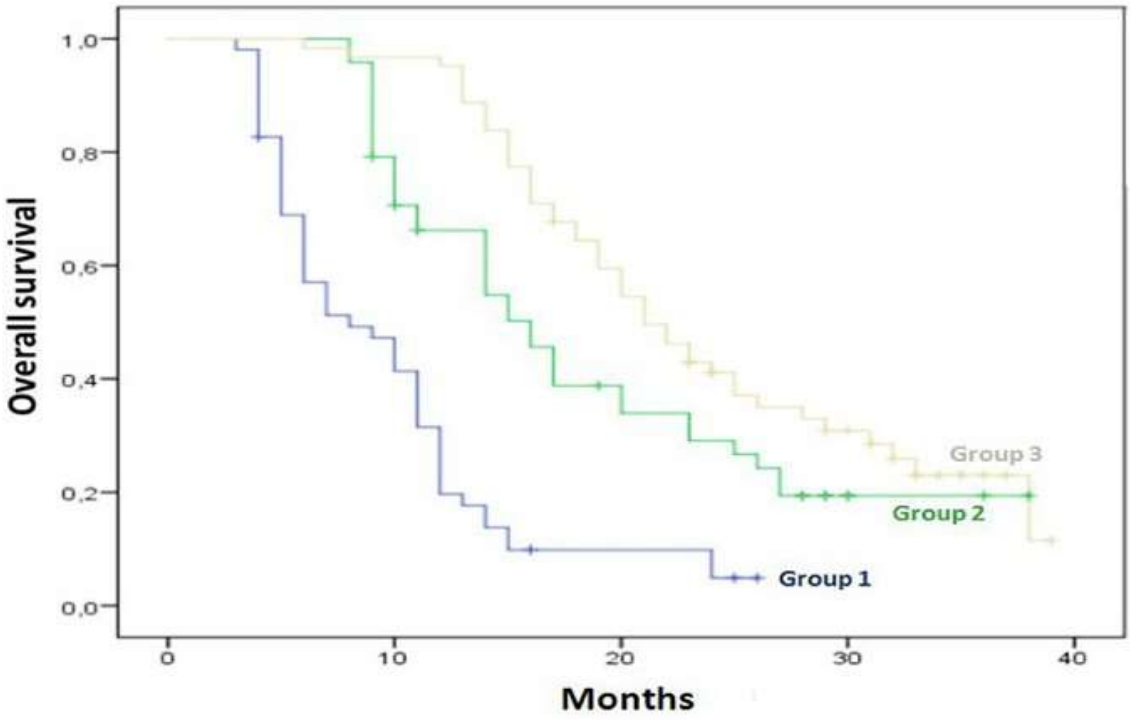
FIGURE LEGENDS AND DESCRIPTIONS

Figure 1. Kaplan Meier curves for overall survival

Two years OS rates were 7.6%, 25% and 32.3% in group 1, 2 and 3, respectively. Kaplan-Meier analysis showed statistically significant difference between OS rates of three groups (*P*<.001 for comparison of group 1 and 2, *P* <.001 for group 1 and 3, *P* =.038 for group 2 and 3).



Pair wise log-rank comparison

	Group 1	Group 2	Group 3
Group 1		p<0.001	p<0.001
Group 2			p=0.038

TABLES

Table 1. Patient characteristics and comparison of patient characteristics of three groups

Patient characteristics	
Age, mean±std	74.4±8.5
Median follow up time, , month (Median(range) and IQR)	40 (9-120) , 36
Gleason grade at initial diagnosis, n(%)	
<8	18(11)
≥8	144(89)
Clinical T stage at initial diagnosis, n(%)	
≤T2	44(27.2)
T3-4	118(72.8)
Type of castration, n(%)	
Medical	114(70.3)
Surgical	48(29.7)
Adding estramustine to docetaxel, n(%)	33(20.3)
Secondary hormonal manipulation, n(%)	
None	82(50.6)
Anti-androgen withdrawal	38(23.4)
Switch to another anti-androgen	42(26)
Presence of bone metastases, n(%)	149(92)
Presence of lymph node metastases, n(%)	62(38.3)

Presence of liver metastases, n(%)	18(11)
Presence of lung metastases, n(%)	18(11)
Time to castration resistance, month (Median(range) and IQR)	18 (3-86) , 23

Parameters	Group 1 (n=52)	Group 2 (n=48)	Group 3 (n=62)	*P* value
Age, mean±std	75.7±8.2	73.3±8.5	74.2±8.8	0.84
Gleason grade at initial diagnosis, n(%)				0.21
<8	6(11.5)	2(4.2)	10(16.2)	
≥8	46(88.5)	46(95.8)	52(83.8)	
Clinical T stage at initial diagnosis, n(%)				0.72
≤T2	15(29.8)	14(29.2)	16(25.9)	
T3-4	37(71.2)	34(70.8)	46(74.1)	
Type of castration, n(%)				0.25
Medical	32(61.5)	34(70.8)	48(77.4)	
Surgical	20(38.5)	14(29.2)	14(22.6)	
Adding estramustine to docetaxel, n(%)	10(19.2)	11(22.9)	12(19.3)	0.78
Secondary Hormonal manipulation, n(%)				0.48
None	28(53.8)	23(47.9)	33(53.2)	
Anti-androgen withdrawal	11(21.2)	10(20.7)	16(25.8)	
Switch to another anti-androgen	13(25)	15(31.2)	13(21)	
Metastases				0,64
M1b Presence of bone metastases , n(%)	48(92.3)	47(97)	54(87)	0,62

M1a, Presence of lymph node metastases, n(%)	26(50)	10(20.8)	26(42)	0,54
M1c, Presence of liver metastases, n(%) Presence of lung metastases, n(%)	4(7.6) 6(11.5)	4(8.3) 4(8.3)	10(16.1) 8(13)	0,68 0,72
Median follow-up,month	46	43	47	0,58
Median nadir PSA value during ADT, (range)	17.7 (0.12-150)	2.3 (0.03-19)	1.2(0.008-7.3)	*0.014
Median PSA value immediately before docetaxel, (range)	93.4 (4-526)	63.7 (4.42-196)	78.1 (1.5-1092)	*0.024
Median nadir PSA value during docetaxel, (range)	65.9 (0.7-400)	34.8 (0.03-161)	18 (0.3-120)	*0.026
Median highest PSA value after starting docetaxel, (range)	153 (4-617)	102.7 (3.2-231)	88.2 (5-490)	*0.037
Median OS, month(range)	7(3-26)	14(8-38)	23(6-39)	*0.016
2 years OS rate, %	7.6	25	32.2	*0.029
Median biochemical PFS, month(range)	3(1-7)	6(1-13)	10(2-19)	*0.04
PSA response to docetaxel, n(%)	16(30.7)	32(66.6)	44(71)	*0.009

ADT, Androgen deprivation therapy; OS, Overall survival; PFS, Progression free survival; PSA, Prostate specific antigen

*Statistically significant

Table 2. Multivariate analysis for prediction of overall survival and response to docetaxel treatment

Variables	Overall survival			Response to docetaxel treatment		
	HR	95% CI	*p* value	HR	95% CI	*P* value
≥8 Gleason grade at initial diagnosis	2.2	1.230-3.547	.001	1.8	1.486-4.342	.003
Higher median nadir PSA value during ADT	0.9	0.702-1.131	0.54	0.9	0.842-1.236	0.5
Higher median PSA value immediately before docetaxel	1.2	0.562-1.634	0.31	1.2	0.674-1.938	0.3
Higher median nadir PSA value during docetaxel	2.3	1.288-5.142	.01	1.9	1.084-4.046	.02
Visceral metastasis	3	1.062-4.328	.001	3.2	1.812-6.326	.001
Time to resistance to ADT	2.8	1.924-3.282	.001	2.2	1.156-4.086	.001

ADT, Androgendeprivationtherapy; PSA, Prostate-specificantigen