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Chemotherapy With Docetaxel Plus Prednisone for Advanced Prostate Cancer: A Retrospective Study of the Time to Clinical Endpoints

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Abstract

Objective: To determine the treatment efficacy of chemotherapy, overall survival of patients with advanced prostate cancer who started initial androgen-deprivation therapy (ADT) then were treated with chemotherapy when hormone-refractory prostate cancer (HRPC) developed.

Materials and Methods: We retrospectively assessed data from medical records of 35 advanced prostate cancer patients who visited at Division of Urology, Department of Surgery, Rajavithi Hospital, Bangkok from 2002 to 2004. Twenty-two patients were included in criteria. Thirteen patients were treated with second-line hormonal therapy (D1) and 9 patients were treated with docetaxel plus prednisone (D2). Both groups were assessed for prostate-specific antigen (PSA) nadir, time to nadir, overall survival since HRPC, overall survival since diagnosis and Kanofsky Performance Status Scale, which were assessed at 6, 12, 24 months after treatment.

Results: ADT was initiated after the diagnosis of advanced prostate cancer in 22 patients. After followed up, the patients who developed HRPC were treated without chemotherapy in D1 group and with chemotherapy in D2 group. Mean PSA nadir was 10.99±15.39 ng/ml and 9.78±14.90 ng/ml. Time to PSA nadir was 10.30±11.37 months and 5±2.78 months. Mean overall survival since HRPC was 19.71±8.57 months and 23.12±12.11 months. Mean overall survival since ADT was 44.14±22.11 months and 33.87± 14.32 months. Mean overall survival since diagnosis was 45±22.32 months and 34.6±14.16 months. Kanofsky Performance Status Scale after 6 months of treatment was 79.23±6.40 and 83.33±7.07, after 12 months was 60±10.80 and 67.5±15.8, after 24 months was 60±10 and 62.5±15 in D1 and D2 patients, respectively.

Conclusions: We described the natural history of advanced prostate cancer in patients who were treated with and without chemotherapy. The results suggested a longer survival and better performance status in chemotherapeutic group.

Keywords: retrospective study, hormone-refractory prostate cancer (HRPC), natural history, prostate-specific antigen (PSA), survival analysis

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Introduction

Our understanding of the role of chemotherapy for advanced prostate cancer has improved considerably in 2004 with the publications of two large randomized phase III trials (SWOG9916[1] and TAX327[2]) and the United States Food and Drug Administration (US FDA) approval of chemotherapy (docetaxel and prednisone) for hormone-refractory prostate cancer (HRPC) have demonstrated improved overall survival as well as clinically significant improvements in endpoints such as quality of life and time to progression. Chemotherapy including mitoxantrone, estramustine and docetaxel are US FDA approved only for use in HRPC and the median survival of patients with symptomatic metastatic HRPC has been 24-36 months.[3]

In general, the definition of HRPC has been the demonstration of progressive disease in the face of castrate levels and a trial of anti-androgen withdrawal over a 4-6 week period if applicable.[4] It may include men with only biochemical failure (two consecutive PSA elevation) and metastatic disease. Regarding this study, we retrospectively assessed efficacy of chemotherapy, overall survival and quality of life of patients with advanced prostate cancer who were started with initial androgen-deprivation therapy (ADT), and were consecutively treated with chemotherapy after HRPC found.

Materials and Methods

We retrospectively assessed data from medical records of 35 patients with advanced prostate cancer who visited at Division of Urology, Department of Surgery, Rajavithi Hospital, Bangkok from 2002-2004 and had PSA documentation and histories of treatment with ADT until HRPC. Thirteen patients were excluded from criteria. Twenty-two patients were enrolment and divided into two groups; the first group, referred as D1, comprising 13 patients treated with second-lined hormonal therapy, and the second group, referred as D2, consisting of 9 patients treated with docetaxel 75 mg. of docetaxel per square meter every three weeks and plus 5 mg of prednisone twice daily prednisolone, after being diagnosed HRPC. *(**Inclusion criteria:** Thai male advanced HRPC patients who were treated with and without chemotherapy and followed up after treatment for at least 24 months. **Exclusion criteria:** patients that have aborted the treatment due to side effects of chemotherapy or poor compliance or loss followed up after treatment).*

We characterized the D1 and D2 cohorts for Gleason score, type of ADT and examined the time to HRPC from starting ADT, prostate-specific antigen (PSA) nadir, time to nadir, overall survival since HRPC, overall survival since diagnosis and quality of life by using Karnofsky Performance Status Scale,[5] which were assessed at 6, 12 and 24 months after treatment for both these cohorts.

Statistical analysis will be performed using of the SPSS version 15.0 for window. Patients' data: age (year), Pathological report (Gleason score), form of ADT, PSA nadir, time to nadir, time to HRPC, overall survival from diagnosis and HRPC and Karnofsky Performance Status Scale (see appendix). We performed a comparison using the two tailed Students t-test and present with mean $\pm$ standard deviation (SD) by table.

Results

The median age at diagnosis in D1 and D2 cohorts were 69 (48-82) and 66 (52-76) years (Table). Amongst the 22 patients, 16 (72%) had metastatic disease to the bone, as shown by uptake of isotope on a bone scan, and 6 (28%) had metastatic lymph node, as confirmed by computed tomography (CT)

scan and 16 patients had PSA >100 at diagnosis, the other had PSA >20 - <100. The median Gleason score for the D1 and D2 patients was 6.54±1.43 and 6±2.58, accordingly. The distribution of Gleason scores for these two subsets of patients is also detailed in *Table.*

Historical hormonal treatment data were collected for both patient cohorts. Men were treated with a GnRH agonist alone, GnRH agonist plus androgen antagonist, orchidectomy alone and orchidectomy plus an androgen antagonist,[6] these data are also given in *Table 1.* ADT was initiated after the diagnosis of advanced disease. After followed up, Mean PSA nadir was 10.99±15.39 ng/ml and 9.78± 14.90 ng/ml, time to PSA nadir was 10.30±11.37 months and 5±2.78 months.

Mean overall survival since HRPC was 19.71± 8.57 months and 23.12±12.11 months. Mean overall survival since ADT was 44.14±22.11 months and 33.87 ±14.32 months. Mean overall survival since diagnosis was 45±22.32 months and 34.6±14.16 months, Kanofsky Performance Status Score after 6 months of treatment was 79.23±6.40 and 83.33±7.07, after 12 months was 60±10.80 and 67.5±15.8 and after 24 months was 60±10 and 62.5±15 in D1 and D2 patients, respectively *(Table).*

Discussion

PSA testing has resulted in a change in the population of patients whose initial hormonal therapy failed. Today, the typical patient presenting with a rising PSA after medical or surgical castration does not have radiographic evidence of metastases.[7] With the development of serum PSA and clinical guidelines for PSA declines as surrogates for clinical response, the development of new drugs for metastatic prostate cancer accelerated.

Docetaxel has been approved for the standard treatment of biochemical failure or first-line treatment of HRPC. It prolongs progression-free and overall survival, improves pain and improves quality of life.[8] In TAX327 trial demonstrated the docetaxel and prednisolone superiority to the past standard, mitoxantrone and prednisone in overall survival 18.9 months vs. 16.5 months and PSA declines greater than 50% were seen in 45-48% of the docetaxel treated patients and 32% of the mitoxantrone treated patients.

Our patients had treated with second-line hormonal therapy (androgen antagonist or ketoconazole) or chemotherapy since HRPC, mean overall survival since HRPC was 19.71±8.57 months in D1 and 23.12±12.11 months in D2, were not significant statistically (p>0.05). Although it showed an insignificant statistical value, the survival in D2 were higher than that in D1 as the publications of two large randomized phase III trials (SWOG 9916[1] and TAX327[2]). Mean overall survival since ADT was 44.14 ±22.11 months in D1 and 33.87±14.32 months in D2. Mean overall survival since diagnosis was 45±22.32 months in D1 and 34.6±14.16 months in D2. These were not the same as overall survival since HRPC, because of the time to HRPC after ADT in D1 were longer than that in D2, resulting in a higher value of overall survival since diagnosis and ADT.

In SWOG9916 Trial, over 85% of patients had a Karnofsky Performance Status over 80% and overall survival was 17.5 months for the combination of docetaxel and estramustine and 15.6 months for mitoxantrone and prednisolone.[9] Regarding this study, we retrospectively assessed the Karnofsky Performance Status from medical record, the results after 6 months of treatment was 79.23±6.40 and 83.33± 7.07, after 12 months was 60±10.80 and 67.5±15.8, after 24 months was 60±10 and 62.5±15 in D1 and D2 patients, respectively. These findings suggested that there were higher performance status scores in chemotherapeutic group. In summary, the overall study

Table 1 *The distribution of age at diagnosis, Gleason scores, form of ADT, time to HRPC and overall survival of D1 and D2 cohorts (number [%] of patients per cohort)*

Variable	D1	D2
Age at diagnosis, years		
76-85	5 (38)	1 (11)
66-75	4 (32)	5 (56)
56-65	3 (23)	2 (22)
<56	1 (7)	1 (11)
PSA at diagnosis		
>100	10 (77)	6 (67)
<100	3 (23)	3 (33)
Bony metastasis	10 (77)	6 (67)
Gleason scores		
2-5	3 (23)	4 (45)
6-7	6 (47)	
8-10	2 (15)	3 (33)
Not known	2 (15)	2 (22)
Mean	6.54 ± 1.43	6 ± 2.58
Form of ADT, hormonal treatment		
GnRH agonist alone		
GnRH agonist plus androgen antagonist	2 (15)	5 (56)
Orchidectomy alone	6 (47)	3 (33)
Orchidectomy plus androgen antagonist	5 (38)	1 (11)
Survival and time to HRPC, months per patient cohort (P)		
Time to PSA nadir	10.30 ± 11.37	5 ± 2.78
PSA nadir	10.99 ± 15.39	9.78 ± 14.90
Time to HRPC from ADT	19.84 ± 12.26	12.44 ± 7.81
Time to HRPC from PSA nadir	11.92 ± 7.95	8.11 ± 6.97
Survival from ADT	44.14 ± 22.11	33.87 ± 14.32
Survival from HRPC	19.71 ± 8.57	23.12 ± 12.11
Overall survival from diagnosis	45 ± 22.32	34.6 ± 14.16
Karnofsky Performance Status Scale		
After 6 month from start treatment	79.23 ± 6.40	83.33 ± 7.07
After 1st year from start treatment	60 ± 10.80	67.5 ± 15.8
After 2nd year from start treatment	60 ± 10	62.5 ± 15
Alive	6 (47)	1 (11)
Death	7 (53)	8 (89)

was not statistically significant, as a result of a retrospective data basis and a small sample size due to insufficient source. However, the study did point out a tendency of increasing survival and good performance status in chemotherapeutic group.

Conclusions

We described the natural history of advanced prostate cancer in patients who were treated with and without chemotherapy. The results suggested a longer survival and better performance status in chemotherapeutic group.

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Appendix

Karnofsky Performance Status Scale Definitions rating (%) Criteria

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead.

Independent SamplesTest

		t-test for equaliyt of means				
		Sig. (2-tailed)	Mean difference	Std. error difference	95% confidence interval of the difference	
		Lower	Upper	Lower	Upper	Lower
Age	Equal variances assumed	.329	3.84615	3.84159	-4.16726	11.85956
	Equal variances not assumed	.304	3.84615	3.64184	-3.75530	11.44761
PSA at diagnosis	Equal variances assumed	.616	.10256	.20125	-.31723	.52235
	Equal variances not assumed	.626	.10256	.20633	-.33527	.54040
Bony metas	Equal variances not assumed	.905	.02564	.21175	41607	.46735
	Equal variances assumed	.906	.02564	.21338	-.42476	.47604
Gleason scores	Equal variances assumed	.571	.54545	.94194	-1.45137	2.54228
	Equal variances not assumed	.623	.54545	1.06809	-1.89674	2.98765
Psa nadir	Equal variances assumed	.856	1.21105	6.59079	-12.53710	14.95920
	Equal variances not assumed	.855	1.21105	6.55089	-12.56708	14.98918
Time to PSA nadir	Equal variances assumed	.188	5.30769	3.89636	-2.81996	13.43535
	Equal variances not assumed	.129	5.30769	3.28858	-1.74519	12.36058
PSA DT	Equal variances assumed	.034	3.42735	1.50875	.28014	6.57456
	Equal variances not assumed	.017	3.42735	1.26632	.70169	6.15301
HRPC from ADT	Equal variances assumed	.127	7.40171	4.64400	-2.28550	17.08892
	Equal variances not assumed	.100	7.40171	4.28437	-1.53756	16.34098
HRPC from PSA nadir	Equal variances assumed	.260	3.81197	3.28503	-3.04048	10.66441
	Equal variances not assumed	.249	3.81197	3.20408	-2.90014	10.52407
Survival from ADT	Equal variances assumed	.299	10.26786	9.49089	-10.23595	30.77167
	Equal variances not assumed	.318	10.26786	9.77425	-11.49486	32.03057
Survival from HRPC	Equal variances assumed	.546	-3.41071	5.50032	-15.29343	8.47200
	Equal variances not assumed	.537	-3.41071	5.37096	-15.05898	8.23755
Overall survival from diagnosis	Equal variances assumed	.295	10.37500	9.51489	-10.18067	30.93067
	Equal variances not assumed	.315	10.37500	9.81120	-11.51091	32.26091
After 6 month from start treatment	Equal variances assumed	.172	-4.10256	2.89641	-10.14438	1.93925
	Equal variances not assumed	.183	-4.10256	2.95150	-10.35358	2.14845
After 1st year from start treatment	Equal variances assumed	.210	-7.50000	5.78591	-19.61004	4.61004
	Equal variances not assumed	.262	-7.50000	6.34227	-21.44917	6.44917
After 2nd year from start treatment	Equal variances assumed	.814	-2.50000	10.10363	-28.47221	23.47221
	Equal variances not assumed	.802	-2.50000	9.46485	-26.85393	21.85393
Alive	Equal variances assumed	.090	.35043	.19680	-.06010	.76095
	Equal variances not assumed	.068	.35043	.18181	-.02890	.72975
Death	Equal variances assumed	.090	-.35043	.19680	-.76095	.06010
	Equal variances not assumed	.068	-.35043	.18181	-.72975	.02890