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Original Article

Predictive factor of androgen deprivation therapy for patients with advanced stage prostate cancer

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ABSTRACT

Background: The purpose of this study was to identify the predictive factors for the efficacy of androgen deprivation therapy (ADT) in men with hormone-sensitive prostate cancer (PC) with or without distant metastasis.

Methods: A retrospective review of PC patients was conducted of the medical records. We enrolled 246 patients who received primary ADT. PC patients treated with ADT for presumed nonlocalized PC were evaluated on the efficacy of ADT using prostate-specific antigen (PSA) time to progression (TTP) and compared factors associated with TTP in patients with distant metastasis and patients without distant metastasis.

Results: A total of 246 patients were treated primarily with ADT. The median follow-up period was 20.2 months. One hundred and ninety-one patients had metastatic disease. The median TTP on ADT for the distant metastasis group was 14.8 months versus 60.1 months in the without distant metastasis group ($P < 0.0001$). In the univariate analysis only, PSA nadir after ADT was associated with longer TTP (hazard ratio, 10.69; 95% confidence interval, 5.56–20.57). In the multivariate analysis, high grade tumor and PSA nadir were independent factors associated with a shorter TTP.

Conclusion: In this study of hormone-sensitive PC patients treated with ADT for nonlocalized PC, high grade tumor and PSA nadir were predicting factors of this treatment.

1. Introduction

Prostate cancer (PC) is the most common cancer diagnosed in genitourinary cancer. The incidence in Thailand is 7.2/100,000 of population and the mortality is 3.7/100,000.[1] In Thailand, patients usually present with advanced stage PC when compared with the USA and Europe.[2] The treatment of choice for patients with advanced stage PC is androgen deprivation therapy (ADT). However, ADT is not curative in patients with locally advanced or metastatic disease.[3–7] Despite the initial response to ADT, most patients will experience disease progression and the development of castration-resistant PC (CRPC).[8,9] The majority of previous studies reported that a longer time to the prostate-specific antigen (PSA) nadir was associated with better survival.[10–12] The predictive factors for the efficacy of ADT in men with hormone-sensitive PC (HSPC) are still unknown. It is important to investigate the prognostic markers that can reflect survival in advanced stage PC. The results may affect the treatment strategy, especially for patients with disease progression.

We queried a longitudinal database of patients treated at Songklanagarind Hospital, Songkhla, Thailand to describe the outcome of ADT use in men with HSPC with or without distant metastases at the time of ADT initiation. Our interest was time to progression (TTP) and factors associated with TTP.

2. Materials and methods

Ethical approval for the study was obtained from the Institutional Review Board of Songklanagarind Hospital. The medical records of all PC patients treated primarily with ADT, either in the form of gonadotropin-releasing hormone agonists or bilateral orchiectomy in Songklanagarind Hospital from 2008 to 2015 were reviewed. We also enrolled patients with locally advanced

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PC and metastatic PC which were not suitable for local treatment. The nadir PSA level was defined as the lowest PSA level after ADT. Disease progression was defined as a 25% increase from the baseline value along with an increase in the absolute value of 2 ng/mL after 12 weeks of treatment.[13] The urologist in charge appointed every patient for clinical examination and serum PSA level every 3 months. A bone scan was used to detect further bone metastases for patients who developed bone pain during ADT treatment. In the case of bone scan progression together with rising PSA, these patients were diagnosed with metastatic RCPC (mCRPC) and went through treatment for mCRPC.

Of 258 patients identified, 246 met all entry criteria. All data were obtained by reviewing the patient histories, imaging studies, operative records, and as discharge summaries. Patients and disease characteristics including age, Gleason score, initial PSA level, bone scan imaging, time of follow-up, mode of ADT, treatment modality upon disease progression, baseline PSA, PSA nadir, and TTP were reviewed.

2.1. Statistical analysis

The statistical analysis was carried out using the R software 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria) and $P < 0.05$ was considered to be statistically significant. The overall survival was estimated by the Kaplan–Meier method. The log rank test was used to assess differences between the groups. The Cox proportional hazards regression model was performed to analyze the independent predictors of TTP. Only the variables that were found to be significant in the univariate analyses ($P < 0.05$) were entered into the multivariate analysis to determine the most significant factors to predict the disease outcome.

3. Results

3.1. Patient characteristics and PSA profile

A total of 246 patients were treated primarily with ADT from January 2008 to May 2015. The characteristics of the patients are shown in Table 1. Overall, 191 patients (77.6%) had metastatic disease at the initiation of ADT treatment. The mean age was 72.7 (± 9) years. The ADT treatment was bilateral orchiectomy in 48.8% of the patients. The median follow-up time was 20 months (range, 11–35 months).

Most patients responded to ADT. The median nadir PSA level was 2.55 ng/mL (range, 0–500 ng/mL). Forty patients (16.3%) reached a nadir PSA < 0.2 ng/mL and 60.6% of patients reached PSA < 4 ng/mL. Most of the PC patients had high grade tumor (54.9%). Only 19 patients had low grade tumor.

The overall TTP was 19 months. In the locally advanced PC group, the TTP was 60.1 months. By contrast, TTP in the metastatic group was 14.8 months. Patients who could not reach a PSA < 4 ng/mL had a TTP of 11.5 months. Table 2 summarizes the association between TTP and disease characteristics. The mean PSA at diagnosis was 354 ng/mL (range, 2–3250 ng/mL). An initial PSA > 50 ng/mL had a TTP of 18.9 months. The TTP in patients with an initial PSA ≤ 50 ng/mL was 25.1 months. Most patients had initial PSA > 50 ng/mL, 89% in the metastatic group and 80% in the locally advanced group. There were no differences in the TTP between the gonadotropin-releasing hormone agonist and surgical castration groups (Table 2).

3.2. Univariate and multivariate analysis of predictor for TTP

With a median follow-up time of 20 months, several factors were identified that predicted TTP after initial ADT treatment on univariate and multivariate analysis (Table 3). The nadir PSA of > 4 ng/mL in high grade tumor was significantly associated with a short TTP (Fig. 1). By contrast, a PSA at diagnosis of ≤ 50 ng/mL was significantly associated with a long TTP.

Table 1
Demographic and clinical characteristics by the primary ADT.

	Overall	Locally advanced	Metastatic disease	*P*
Mean age (yr)	72.7	74.7	72.1	0.059
Gleason score				0.774
≤ 6	19	4	15	
7	92	23	69	
8–10	135	28	107	
Median base line PSA (ng/mL)	297	115	476	< 0.001
Follow-up (mo)	20.2	35.4	18.1	< 0.001
Mode of ADT				0.011
GnRH agonist	126	37	89	
Bilateral orchiectomy	120	18	102	
Median nadir PSA	2.5	0.5	3.6	< 0.001
Median TTP (mo)	19	60.1	14.8	< 0.001

ADT, androgen deprivation therapy; PSA, prostate-specific antigen; TTP, time to progression.

Table 2
Association between time to progression (TTP) and disease characteristics.

	Overall	Locally advanced	Metastatic disease
Gleason score			
≤ 6	37.5	47.8	37.5
7	27.9	69.9	18.1
8–10	14.8	52.7	12.5
Initial PSA			
≤ 50	25.1	47.8	22.1
> 50	18.9	60.1	14.8
PSA nadir			
≤ 0.2	N/A	N/A	43.5
0.2–4	23.7	52.7	19.0
> 4	11.5	38.5	10.4
Mode of ADT			
Medical ADT	18.9	69.6	14.3
Surgical ADT	19.8	53.7	15.9

ADT, androgen deprivation therapy; PSA, prostate-specific antigen.

Table 3
Hazard ratio estimates and confidence intervals from proportional hazards modeling of time to progression (TTP).

Overall				
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Gleason score				
≤ 6	1	0.013	1	0.003
7	1.25 (0.61–2.54)		1.84 (0.86–3.91)	
8–10	1.92 (0.97–3.8)		2.72 (1.31–5.64)	
Mode of ADT		0.428		0.636
Orchiectomy	1		1	
GnRH agonist	0.88 (0.64–1.2)		1.08 (0.78–1.49)	
Initial PSA		0.635		0.059
≤ 50	1		1	
> 50	1.13 (0.69–1.84)		0.58 (0.33–0.99)	
PSA nadir				
≤ 0.2	1	< 0.001	1	< 0.001
0.2–4	3.81 (1.98–7.31)		4.01(2.08–7.73)	
> 4	10.69 (5.56–20.57)		12.19(6.25–23.77)	

ADT, androgen deprivation therapy; CI, confidence interval; GnRH, gonadotropin-releasing hormone agonist; HR, hazard ratio; PSA, prostate-specific antigen.