Clinical outcomes of anti-androgen withdrawal and subsequent alternative anti-androgen therapy for advanced prostate cancer following failure of initial maximum androgen blockade

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Abstract. The present study aimed to investigate the significance of anti-androgen withdrawal and/or subsequent alternative anti-androgen therapy in patients with advanced prostate cancer (PC) who relapsed after initial maximum androgen blockade (MAB). The present study evaluated the clinical outcomes of 272 consecutive advanced PC patients undergoing anti-androgen withdrawal and/or subsequent alternative anti-androgen therapy with flutamide following the failure of initial MAB using bicalutamide. With the exception of 41 patients (15.1%) who did not undergo anti-androgen withdrawal due to the characteristics of PC suggesting aggressive diseases, prostate-specific antigen (PSA) declined from the baseline value in 83 patients (35.9%), including 18 (7.8%) with PSA decline >50%, but not in the remaining 148 (64.1%). No significant difference in the overall survival (OS) or cancer-specific survival (CSS) among the three groups was observed based on the response to anti-androgen withdrawal. Following the introduction of alternative anti-androgen therapy with flutamide, PSA decline was observed in 185 patients (68.0%), including 103 (37.9%) who achieved a PSA reduction of >50%; however, the PSA level continued to elevate in the remaining 87 (32.0%). Furthermore, of the numerous factors examined, only the duration of the initial MAB therapy was shown to be significantly correlated with the PSA decline following alternative anti-androgen therapy. Multivariate analysis of several factors identified revealed that only PSA decline following alternative anti-androgen therapy was an independent predictor of CSS and OS. If initial MAB is effective, the introduction of alternative anti-androgen therapy may be considered; however, anti-androgen withdrawal should be omitted, irrespective of the characteristics of advanced PC.

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Introduction

Prostate cancer remains the most frequently diagnosed malignancy and the second leading cause of cancer-associated mortality in men in Western industrialized countries (1). Despite the notably prolonged survival in patients with prostate cancer, improved survival in patients with advanced disease has not significantly contributed to this decline in mortality (2). Although intensive efforts have been made in the field of prostate cancer research, androgen withdrawal therapy is still the only effective treatment for men with advanced prostate cancer. Initially, 80-90% of such patients favorably respond to this therapy; however, disease progression to lethal stage eventually occurs in the majority of these patients within a few years under the low levels of serum testosterone, which is recognized as castration-resistant prostate cancer (CRPC) (3).

Historically, prior to the introduction of docetaxel, no agents demonstrated survival benefits in patients with CRPC (4,5); therefore, the usefulness of different types of hormonal therapy had been investigated to prolong the duration until the appearance of a phenotype characteristic of CRPC (6,7). For example, anti-androgen withdrawal syndrome, a manifestation of a prostate-specific antigen (PSA) decline, brought about by the discontinuation of the administration of anti-androgen, has been observed in 20-30% of patients receiving maximum androgen blockade (MAB) (8,9). In addition, several previous studies have reported a favorable PSA response to alternative anti-androgen therapy in advanced prostate cancer, which relapsed following initial MAB (8,10-14). Along with docetaxel, several novel agents with different mechanisms of action, including abiraterone, enzalutamide and cabazitaxel, have been shown to yield positive results in phase III trials against metastatic CRPC, and are already widely used in clinical practice (15,16).

Considering these findings, it is important to reevaluate the significance of the continuous treatment of patients with advanced prostate cancer with secondary hormonal therapy following the failure of initial MAB in order to determine whether such a strategy remains suitable now that several novel agents against CRPC have become available. The present study, therefore, retrospectively reviewed the clinical outcomes in a total of 272 consecutive patients with advanced prostate cancer who underwent anti-androgen withdrawal and/or subsequent

alternative anti-androgen therapy with flutamide following the failure of initial MAB, using bicalutamide.

Patients and methods

Patients. The present study included a total of 272 consecutive patients with histologically diagnosed advanced prostate cancer, who underwent anti-androgen withdrawal and/or alternative anti-androgen therapy following the failure of initial MAB using bicalutamide, between January 2010 and September 2014. In all patients, serum PSA levels were measured at least every 12 weeks. Clinical variables were evaluated based on the findings of digital rectal examination, transrectal ultrasonography (TRUS), systematic TRUS-guided needle biopsy, pelvic computed tomography, magnetic resonance imaging and bone scan, and were determined according to the 2010 Tumor Node Metastasis classification system. Treatment failure was defined as increased serum PSA levels on three successive occasions, and the response duration was regarded as the duration from the start of each treatment until failure.

Hormonal therapy. In this series, all patients were initially treated with MAB consisting of either bilateral orchidectomy or medical castration using a luteinizing hormone-releasing hormone agonist (goserelin acetate or leuprorelin acetate) plus bicalutamide (80 mg/day) as first-line hormonal therapy. When the first-line therapy was judged to have failed, bicalutamide was discontinued to determine whether or not androgen withdrawal syndrome was observed in certain patients without characteristics suggesting aggressive disease, including the presence of bone metastasis at diagnosis, high Gleason score, short PSA doubling time and/or short duration of initial MAB therapy. Subsequent second-line MAB using flutamide (375 mg/day) as an alternative anti-androgen was initiated in all patients, irrespective of the evaluation of the androgen withdrawal response.

Statistical analysis. All statistical analyses were performed using Statview 5.0 software (Abacus Concepts, Inc., Berkeley, CA, USA). Differences between the two groups were analyzed using the chi-squared test or unpaired t-test. The overall survival (OS) and cancer-specific survival (CSS) rates were calculated using the Kaplan-Meier method, and the differences were determined by the log-rank test. The prognostic significance of certain factors was assessed using the Cox proportional hazards regression model. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Table I shows the characteristics of the 272 patients included in the present study. As shown in Fig. 1, during the observation period of the present study from the introduction of initial MAB (median, 42.3 months), overall and cancer-specific mortality occurred in 58 (21.3%) and 41 (15.0%), respectively, and the 5- and 10-year OS rates were 73.3 and 66.8%, respectively, while the 5- and 10-year CSS rates were 79.2 and 72.5%, respectively.

Once the initial MAB using bicalutamide had failed, the incidence of anti-androgen withdrawal syndrome was assessed in 231 (84.9%) of the 272 patients; however, the observation of anti-androgen withdrawal syndrome was omitted in the remaining 41 (15.1%) due to characteristics suggesting the presence of aggressive diseases. A decline in the serum PSA level following anti-androgen withdrawal was observed in 83 (35.9%) of the 231 patients, and >50% decline from the baseline serum PSA level was observed in 18 patients (7.8%). Of several factors examined by univariate analysis, no factor significantly correlated with PSA decline by anti-androgen withdrawal therapy (data not shown). Furthermore, when the included patients were classified into the following three groups: i) 41 patients without assessment of anti-androgen withdrawal syndrome; ii) 83 with PSA decline; iii) 148 without PSA decline following anti-androgen withdrawal therapy, no significant difference in the OS or CSS was observed among the groups (Fig. 2).

Following the introduction of alternative anti-androgen therapy using flutamide, PSA decline was observed in 185 patients (68.0%), among whom 103 (37.9%) were regarded as responders exhibiting a reduction of PSA >50%; however, the PSA level continued to increase in the remaining 87 (32.0%). Although no significant difference was observed in the OS or CSS between 103 patients with PSA decline >50% and 82 with that of 0-50%, both the OS and CSS in 87 patents without PSA decline were significantly poorer compared with the 103 and 83 patients showing PSA decline >50% and 0-50%, respectively (Fig. 3). Furthermore, as shown in Table II, of several factors examined, only the duration of initial MAB therapy was shown to be significantly correlated with whether or not PSA declined following alternative anti-androgen therapy.

Table I. Patient characteristics.

Characteristic	Patient details
Median age (years)	72 (47-89)[a]
Median initial PSA (ng/ml)	120.9 (1.3-22,412.1)[a]
Biopsy Gleason score	
≤7	49 (18.0)[b]
8-10	223 (82.0)[b]
T category	
T1 or T2	45 (16.6)[b]
T3	169 (62.1)[b]
T4	58 (21.3)[b]
N category	
N0	145 (53.3)[b]
N1	127 (46.7)[b]
M category	
M0	91 (33.5)[b]
M1	181 (66.5)[b]
Median PSA nadir during initial MAB (ng/ml)	0.30 (<0.001-550.3)[a]
Median duration of initial MAB (months)	15.0 (1-180)[a]

[a]Range; [b]Percentage. PSA, prostate-specific antigen; MAB, maximum androgen blockade; T, tumor; N, node; M, metastasis.

Table II. Association between several factors and PSA decline following alternative anti-androgen therapy.

	PSA decline following alternative anti-androgen withdrawal		
	Yes (n=185)	No (n=87)	P-value
Median age (years)	72 (47-89)[a]	72 (54-87)[a]	0.79
Median initial PSA (ng/ml)	167.3 (1.3-22,412.1)[a]	92.4 (3.4-6,305.8)[a]	0.35
Biopsy gleason score			0.63
≤7	33 (17.8)[b]	16 (18.4)[b]	
8-10	152 (82.2)[b]	71 (81.6)[b]	
T category			0.34
T1 or T2	31 (16.8)[b]	14 (16.1)[b]	
T3 or T4	154 (83.2)[b]	73 (83.9)[b]	
N category			0.71
N0	99 (53.5)[b]	46 (52.9)[b]	
N1	86 (46.5)[b]	41 (47.1)[b]	
M category			0.65
M0	61 (33.0)[b]	30 (34.5)[b]	
M1	124 (67.0)[b]	57 (65.5)[b]	
Median PSA nadir during initial MAB (ng/ml)	0.25 (<0.003-47.6)[a]	0.63 (0.007-476.4)[a]	0.16
Median duration of initial MAB (months)	16.9 (2.3-179.1)[a]	11.7 (1.1-135.9)[a]	0.016
PSA decline following anti-androgen withdrawal			0.31
Yes	54 (29.2)[b]	29 (33.3)[b]	
No	114 (61.6)[b]	34 (39.1)[b]	
Not assessed	17 (9.2)[b]	24 (27.6)[b]	

[a]Range; [b]Percentage. PSA, prostate-specific antigen; MAB, maximum androgen blockade.

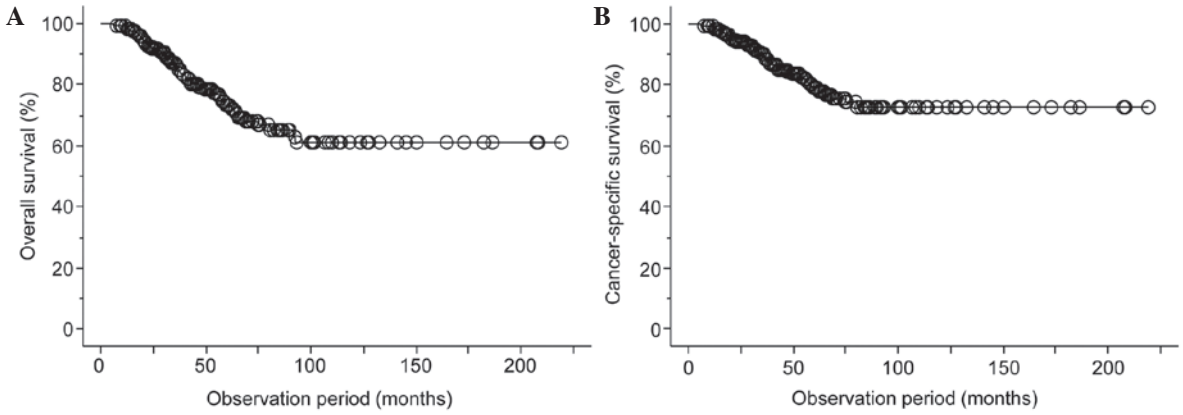

Figure 1. (A) Overall survival and (B) cancer-specific survival of the 272 patients with advanced prostate cancer who underwent anti-androgen withdrawal and/or alternative anti-androgen therapy.

The present study subsequently performed uni- and multivariate analyses to identify factors predicting the OS and CSS in the 272 patients. Univariate analyses identified the following significant prognostic predictors: PSA nadir during initial MAB, duration of initial MAB therapy and PSA decline following alternative anti-androgen therapy for OS, and positive for M category, PSA nadir during initial MAB, duration of initial MAB therapy and PSA decline following alternative anti-androgen therapy for CSS. However, only PSA decline following alternative anti-androgen therapy was shown to be independently associated with both the OS and CSS by multivariate analysis (Table III). Figure 4 highlights the OS and CSS curves, according to PSA decline after alternative anti-androgen therapy.

Discussion

Until the introduction of docetaxel (4,5), no standard approach existed for patients with advanced prostate cancer if first-line

Table III. Univariate and multivariate analyses of associations between various parameters with cancer-specific and overall survival in 272 patients with advanced prostate cancer who underwent anti-androgen withdrawal and/or alternative anti-androgen therapy.

	Overall survival				Cancer-specific survival			
	Univariate		Multivariate		Univariate		Multivariate	
Variables	Hazard ratio	P-value	Hazard ratio	P-value	Hazard ratio	P-value	Hazard ratio	P-value
Age[a] (<70, vs. 70≤)	0.56	0.770	-	-	0.80	0.2300	-	-
Initial PSA[b] (<100, vs. 100≤)	1.11	0.530	-	-	1.37	0.3000	-	-
Biopsy Gleason score (≤7, vs. 8-10)	1.39	0.390	-	-	1.13	0.2900	-	-
T category (T1/T2, vs. T3/T4)	1.20	0.680	-	-	1.14	0.4800	-	-
N category (N0, vs. N1)	1.13	0.490	-	-	1.20	0.4400	-	-
M category (M0, vs. M1)	1.52	0.055	-	-	2.65	0.0097	2.33	0.210
PSA nadir during initial MAB[b] (<2, vs. 2≤)	0.47	0.031	1.21	0.11	0.99	0.0130	0.97	0.260
Duration of initial MAB[c] (<24, vs. 24≤)	0.53	0.019	0.72	0.38	0.25	0.0300	0.70	0.310
PSA decline after anti-androgen withdrawal (yes, vs. no/not assessed).	0.88	0.500			0.99	0.8500	-	-
PSA decline after alternative anti-androgen therapy (yes, vs. no)	0.31	<0.001	0.33	0.029	0.21	<0.001	0.28	0.001

[a]years; [b]ng/ml; [c]months. PSA, decline after alternative anti-androgen; MAB, maximum androgen blockade.

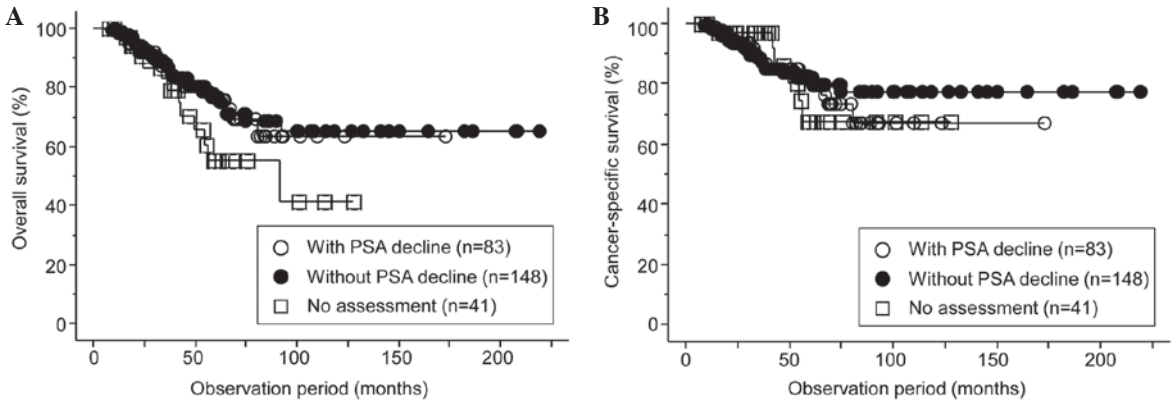

Figure 2. (A) Overall survival and (B) cancer-specific survival of the 272 patients with advanced prostate cancer who underwent anti-androgen withdrawal and/or alternative anti-androgen therapy, according to the PSA response to anti-androgen withdrawal. PSA, prostate-specific antigen.

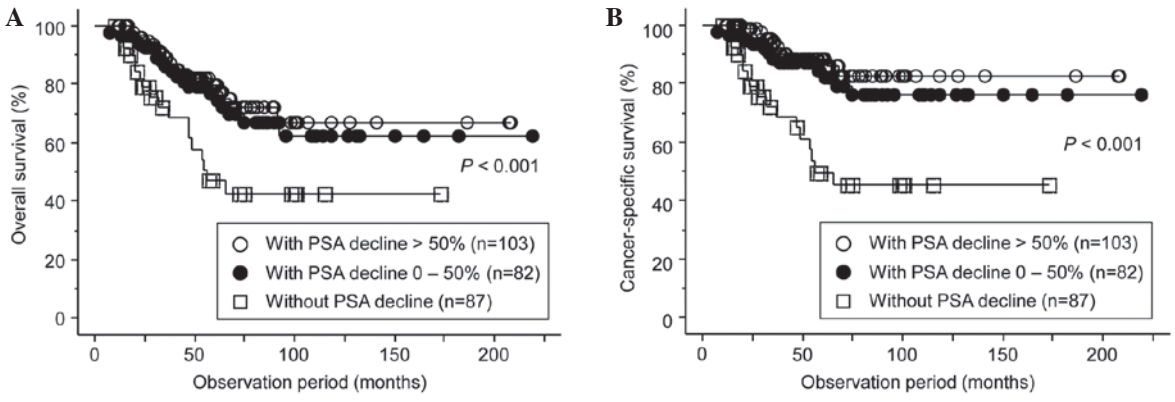

Figure 3. (A) Overall survival and (B) cancer-specific survival of the 272 patients with advanced prostate cancer who underwent anti-androgen withdrawal and/or alternative anti-androgen therapy, according to the degree of the PSA response to alternative anti-androgen therapy. PSA, prostate-specific antigen.

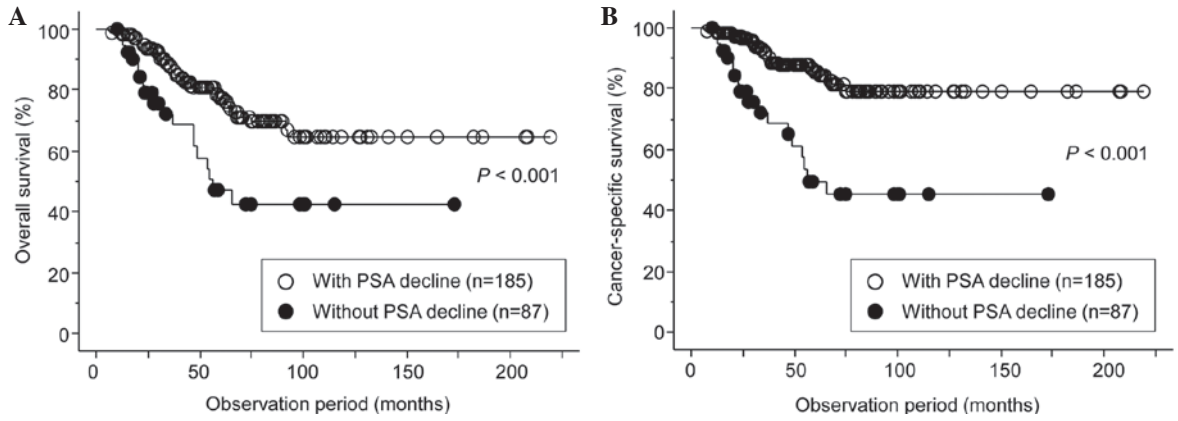

Figure 4. (A) Overall survival and (B) cancer-specific survival of the 272 patients with advanced prostate cancer who underwent anti-androgen withdrawal and/or alternative anti-androgen therapy according to the PSA decline in response to alternative anti-androgen therapy. PSA, prostate-specific antigen.

hormonal therapy failed. Therefore, whether several secondary approaches using hormonal agents improved the prognosis of such patients was previously investigated (6,7). Of these, anti-androgen withdrawal and alternative anti-androgen therapy became regarded as comparatively useful options for prostate cancer patients following the failure of initial MAB (8-14). In recent years, however, novel agents with different mechanisms of action against CRPC have been approved and widely introduced into clinical practice, resulting in a marked paradigm shift in the therapeutic strategy for advanced prostate cancer (15,16). Taken together, it is important to re-analyze the significance of secondary hormonal therapy, which, despite the lack of high levels of evidence, have been reported to exhibit certain beneficial effects on the prognosis of patients with advanced prostate cancer. The present study retrospectively assessed the clinical outcomes in a total of 272 Japanese men with advanced prostate cancer who underwent anti-androgen withdrawal and/or subsequent alternative anti-androgen therapy following the failure of initial MAB.

In this series, considering the relatively low incidences of anti-androgen withdrawal syndrome in previous studies (8-10), 12.9% of patients judged to have aggressive disease did not undergo anti-androgen withdrawal therapy. However, the proportion of patients exhibiting anti-androgen withdrawal syndrome remained low even following the exclusion of patients without the assessment of anti-androgen withdrawal syndrome; that is, PSA decline >50% following anti-androgen withdrawal was observed in only 7.8% of patients. Furthermore, the present study failed to identify any parameter significantly correlated with the PSA decline by anti-androgen withdrawal therapy, suggesting that it is difficult to identify patients who are likely to benefit from this therapy. Collectively, these findings suggested that confirming the anti-androgen withdrawal response in patients with prostate cancer showing relapse following initial MAB cannot be positively recommended.

In the present study, MAB using flutamide was applied to all patients as alternative anti-androgen therapy, and a reduction in the PSA level was observed in 68.0% of the patients. When the response was defined as a decrease of >50% in the PSA level, 30.1% of patients were regarded as responders. This outcome of alternative anti-androgen therapy is comparable with those previously reported (8,10-14). For example, Kassouf *et al* (14) noted a PSA decrease >50% in 29% of patients following second-line hormonal therapy with nilutamide, while Suzuki *et al* (8) reported that 35.8% of patients treated with non-steroidal anti-androgens as alternative therapy, achieved PSA decline >50%. These findings indicated the definitive effect of alternative anti-androgen therapy, irrespective of introduced agents, on the PSA decline in patients with advanced prostate cancer.

In the present series, no significant difference was observed in the OS or CSS between 103 patients with PSA decline >50% and 82 with that of 0-50% following alternative anti-androgen therapy. The present study, therefore, assessed the impacts of several parameters on whether or not the PSA decline could be achieved by alternative anti-androgen therapy. Of several factors examined, only the duration of initial MAB was shown to be significantly correlated with the induction of PSA decline by alternative anti-androgen therapy. Previous studies identified certain variables associated with the response to alternative anti-androgen therapy, including the baseline serum PSA level, presence of bone metastasis and anti-androgen withdrawal response, in addition to the duration of initial MAB (8,10,11,14). These findings suggested that alternative anti-androgen therapy can promote a favorable response in patients with prostate cancer with comparatively indolent characteristics and limited disease extension. Furthermore, whether or not PSA decline was achieved following alternative anti-androgen therapy was identified as the only independent predictor of both the OS and CSS in the 272 patients included in the present study. This finding was supported by a previous study demonstrating the potential value of the response to alternative anti-androgen therapy to assess the prognosis following the failure of initial MAB (8).

The present study had several limitations. Firstly, despite being one of the largest series evaluating the outcomes of second-line hormonal therapy using alternative anti-androgen, this was a retrospective study including only Japanese men. Secondly, the indication of anti-androgen withdrawal therapy was not determined based on a strict criterion, which may have affected the present outcomes, even slightly. Finally, the outcomes of the present study should be carefully interpreted

considering that no patient was included who received agents demonstrated to have prognostic benefits in CRPC patients, with the exception of docetaxel.

In conclusion, following the failure of initial MAB, it may not be necessary to evaluate anti-androgen withdrawal irrespective of the characteristics of patients with advanced prostate cancer, whereas if initial maximum androgen blockade is effective, alternative anti-androgen therapy may be considered. However, it should be prospectively investigated whether or not alternative anti-androgen therapy would be superior to the direct introduction of currently approved agents against CRPC followed by initial MAB.

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