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A prospective, multicenter study on the clinical effectiveness of abiraterone in metastatic castration-resistant prostate cancer in Korea: Pre- vs. post-chemotherapy

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Purpose: The proper treatment sequence for administering abiraterone acetate plus prednisolone (AAP) and chemotherapeutic agents has not yet been elucidated for metastatic castration-resistant prostate cancer (mCRPC). Hence, this study evaluated the effectiveness and safety of AAP in pre- and post-chemotherapy settings using real-world data.

Materials and Methods: This prospective, multicenter, open-label, observational study included 506 patients with mCRPC. Patients were classified according to the timing of chemotherapy into pre- and post-chemotherapy groups. The effectiveness and safety of AAP were compared between the groups; the prostate-specific antigen (PSA) response, PSA progression-free survival, and radiologic progression-free survival were assessed; and adverse drug reactions were recorded.

Results: Among the included patients, 319 and 187 belonged to the pre- and post-chemotherapy groups, respectively. Risk classification was similar between the two groups. The PSA response was 61.8% in the pre-chemotherapy group and 39.0% in the post-chemotherapy group ($p<0.001$). The median time to PSA progression (5.00 vs. 2.93 mo, $p=0.001$) and radiologic progression-free survival (11.84 vs. 9.17 mo, $p=0.002$) were significantly longer in the pre-chemotherapy group. Chemotherapy status was associated with PSA (hazard ratio [HR] 1.39, 95% confidence interval [CI] 1.09–1.77) and radiologic progression (HR 1.66, 95% CI 1.18–2.33) during AAP treatment. Adverse drug reactions were reported at similar frequencies in both groups.

Conclusions: In this postmarketing surveillance, AAP benefited patients with mCRPC, especially in settings before chemotherapy was administered, resulting in a high PSA response and longer PSA and radiologic progression-free survival with tolerable adverse drug reactions.

Keywords: Abiraterone; Prostate cancer; Prostate-specific antigen; Real-world data

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INTRODUCTION

Prostate cancer is the most prevalent cancer in men, after skin cancer, and in addition to the 3.3 million existing patients in the United States, is newly diagnosed in 160,000 men annually [1]. Although prostate-specific antigen (PSA) screening has led to the early detection of prostate cancer, advanced or metastatic prostate cancer remains a life-threatening disease [2]. Therapeutic strategies for metastatic prostate cancer are mainly based on androgen deprivation treatment (ADT), which targets androgen receptors and their corresponding signals [1]. ADT is the standard adjuvant treatment for locally advanced cancer or metastatic castration-sensitive prostate cancer [3,4].

However, resistance to ADT leads to the emergence of metastatic castration-resistant prostate cancer (mCRPC). Resistance mechanisms include amplification, mutations, splicing variants, and aberrant activation of androgen receptors [5]. The second-generation androgen inhibitor, abiraterone acetate, was developed as a prodrug to deliver abiraterone, which inhibits cytochrome P450c17 and suppresses the biosynthesis of androgen from the adrenal gland, testes, and prostate cancer cells [6]. In mCRPC, cytochrome P450c17 levels increase to facilitate the *de novo* synthesis of androgen [7]. Abiraterone acetate is metabolized to abiraterone, which blocks cytochrome P450c17 expression to prevent the *de novo* synthesis of androgens and hence efficiently suppresses disease progression [8]. The use of abiraterone plus prednisolone has expanded from post-chemotherapy mCRPC to metastatic hormone-sensitive prostate cancer [9]. In 2011, the COU-AA-301 trial demonstrated that abiraterone acetate plus prednisolone (AAP) plus ADT increased overall survival in mCRPC after docetaxel treatment [6,10]. In 2013, it was reported that AAP plus ADT prolonged radiographic progression-free survival (rPFS) and overall survival in mCRPC before chemotherapy and delayed the initiation of chemotherapy [4]. In 2017, the STAMPEDE and LATITUDE trials showed that AAP plus ADT significantly delayed overall survival compared with ADT alone in patients with metastatic hormone-sensitive prostate cancer [11,12]. AAP plus ADT also improved PSA PFS and quality of life in patients with mCRPC before or after docetaxel-based chemotherapy [4,6,13]. However, the proper treatment sequence of AAP and chemotherapy for mCRPC has not yet been elucidated. Moreover, it is unclear whether AAP has similar effectiveness in mCRPC before and after chemotherapy in patients with different tumor populations, disease burdens, and general conditions. In the present postmarketing surveillance study, we aimed to evaluate the effectiveness of AAP in chemotherapy-naïve patients vs. patients previously treated with chemotherapy and the safety and adverse events following treatment.

MATERIALS AND METHODS

1. Study design and participants

This prospective, multicenter, open-label, observational study was conducted at 60 centers in South Korea from July 2012 to June 2021. This study was performed in accordance with the principles of the Declaration of Helsinki, and the study protocol was approved by the Institutional Review Boards of all study centers. The approval number from the Institutional Review Board of Seoul National University Hospital was H-1607-142-778. Informed consent was obtained from all participants.

This study enrolled patients aged 18 years or older who were newly or currently prescribed AAP for prostate cancer based on local labels. The exclusion criteria for the study were patients with contraindications to AAP, such as those with severe hepatic impairment, a history of hypersensitivity to AAP, or genetic conditions such as Lapp lactase deficiency or glucose-galactose malabsorption. Patients who signed an informed consent form to agree to the use of relevant personal information and who were willing to participate in postmarketing surveillance were included in the analysis. Patients were administered 1,000 mg of abiraterone orally once daily in combination with prednisolone as an initial treatment. Adherence and adverse events were evaluated at every follow-up visit during the study period.

2. Outcomes measured

The primary objective of this study was to evaluate the effect of AAP in patients with mCRPC who had not received prior chemotherapy (i.e., the pre-chemotherapy group) or who had received chemotherapy previously (i.e., the post-chemotherapy group) in clinical practice in Korea. The effectiveness endpoints were PSA response and progression, rPFS, and overall response assessment by the investigator. PSA response was defined as a greater than 50% reduction in baseline PSA levels after AAP treatment. PSA progression was defined as an increase in the PSA level of more than 25% over the nadir and of at least 2 ng/mL. rPFS was defined as objective evidence of radiological progression or death. Similar to the LATITUDE trial, high- and low-risk patients were stratified and compared between the two groups. High risk was defined as harboring any two of the following features: (a) a Gleason score of eight or higher, (b) 3 or more bone metastasis sites, and (c) measurable visceral metastasis [8].

All drug reactions and adverse events following exposure

were systematically recorded, regardless of seriousness or causality, from the first use of AAP within the study period to within 30 days of the patient's last use of AAP. Adverse events were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.3.

3. Statistical analyses

Continuous variables, including follow-up duration, disease duration, age at enrollment, age at diagnosis, disease duration, and PSA level, were presented as descriptive statistics (mean and standard deviation) and were analyzed using Wilcoxon's rank-sum test or two-sample t-test based on the findings of the Shapiro–Wilk test, which is a normality test. Otherwise, categorical variables were described as frequencies with percentages and were analyzed using the chi-squared test or Fisher's exact test. For time-to-event variables, PSA PFS and rPFS were estimated using the Kaplan–Meier method and the log-rank test. The Cox regression model using associated factors was used to assess the statistical significance of the observed difference in estimated survival between the study groups. All p-values less than 0.05 were considered statistically significant. Statistical analyses were performed using the SAS software version 9.4 (SAS Institute Inc.).

RESULTS

1. Patient characteristics

Between December 21, 2016 and January 19, 2021, from the 60 participating centers in Korea, 608 patients were enrolled in this postmarketing surveillance and were followed-up for the registry system. Of the patients assessed for eligibility, 40 were excluded because of violation of the dosage regimen, and of those enrolled in the study, 62 were excluded because of missing more than one clinical assessment. Finally, 506 patients with prostate cancer were included in the analysis (Fig. 1).

mCRPC patients were grouped according to the AAP treatment sequence as receiving treatment before (pre-) or after (post-) chemotherapy; 319 patients were included in the pre-chemotherapy group and 187 in the post-chemotherapy group. The mean follow-up duration was longer in the pre-chemotherapy group than in the post-chemotherapy group (32.8 vs. 27.0 wk, p=0.001). The mean age at diagnosis was lower in the post-chemotherapy group than in the pre-chemotherapy group (69.7 vs 67.4 y, p=0.003). Disease duration was longer in the post-chemotherapy group than in the pre-chemotherapy group (4.9 vs. 3.9 y, p<0.001). Bone and lymph nodes were the most prevalent metastatic sites in both groups. The bone metastasis burden was higher in the post-chemotherapy group than in the pre-chemotherapy group because 30.4% of patients had bone metastasis with over 10 lesions (p=0.012). The Gleason score at initial diagnosis was similar between the two groups. The baseline PSA level at enrollment was higher in the post-chemotherapy group than in the pre-chemotherapy group (24.6 vs. 51.7, p=0.004). Definitive therapy was performed in both groups, with equal frequencies of radical prostatectomy or radiation therapy. In the post-chemotherapy group, docetaxel was primarily included in the chemotherapy regimen in the majority of patients (99.5%).

Baseline comorbidities at enrollment, including cardiac, liver, kidney, and allergic disorders, were similar between the two groups. Risk classification did not differ significantly between the two groups (high-risk, 58.6% vs. 63.1%, p=0.320). The treatment duration with AAP was longer in the pre-chemotherapy group than in the post-chemotherapy group (6.6 vs. 4.9 mo, p=0.004) (Table 1).

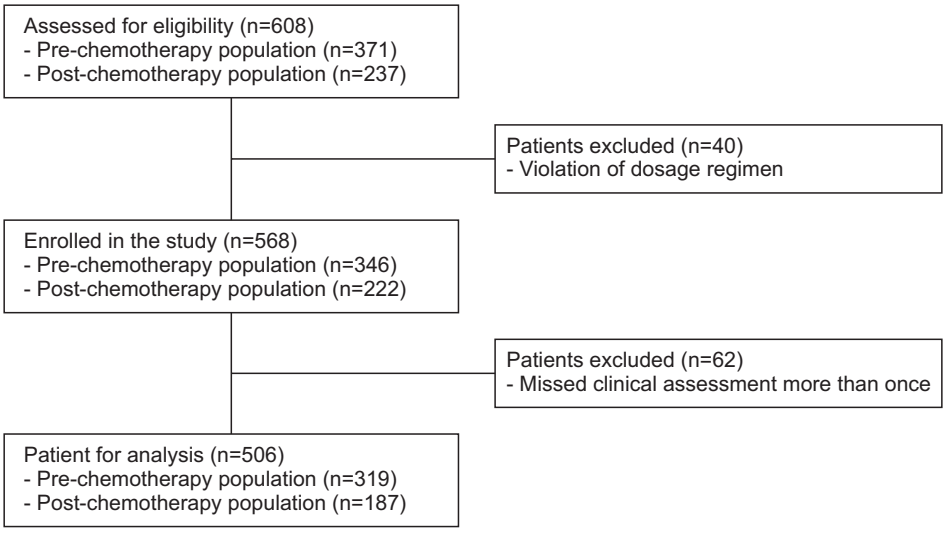

Fig. 1. The patient flow of the study.

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Table 1. Demographic and baseline clinical characteristics of the patients

Variable	Pre-chemotherapy (n=319)	Post-chemotherapy (n=187)	p-value
Follow-up duration (wk)	32.8±20.53	27.0±19.09	0.001
Age (y)	73.7±8.61	72.4±7.77	0.068
Age at diagnosis (y)	69.7±8.30	67.4±8.17	0.003
Disease duration (y)	3.9±3.69	4.9±3.62	<0.001
Metastasis site[a]			
Soft tissue	41 (12.9)	32 (17.1)	0.188
Lymph node	164 (51.4)	105 (56.1)	0.303
Bone	258 (80.9)	161 (86.1)	0.133
Liver	10 (3.1)	8 (4.3)	0.503
Lung	25 (7.8)	16 (8.6)	0.775
Other	30 (9.4)	13 (7.0)	0.340
Number of bone metastases			0.012
1	33 (12.8)	16 (9.9)	
2	35 (13.6)	13 (8.1)	
3	26 (10.1)	9 (5.6)	
4-9	110 (42.6)	73 (45.3)	
≥10	47 (18.2)	49 (30.4)	
Unknown	7 (2.7)	1 (0.6)	
Gleason score			0.237
≤6	5 (1.6)	1 (0.5)	
7	27 (8.5)	18 (9.6)	
8	107 (33.5)	52 (27.8)	
9	132 (41.4)	72 (38.5)	
10	28 (8.8)	26 (13.9)	
Baseline PSA	24.6 (0.2–3,704.3)	51.7 (0.0–5,001.0)	0.004
Definitive treatment[a]			
Radical prostatectomy	60 (18.8)	43 (23.0)	0.259
Radiation therapy	59 (18.5)	29 (15.5)	0.392
Comorbidity			0.864
Yes	216 (67.7)	128 (68.5)	
Cardiac disorder	121 (56.0)	70 (54.7)	
Liver disorder (Child-Pugh)[a]	8 (3.7)	8 (6.3)	
Class A	8 (100.0)	8 (100.0)	
Class B	1 (12.5)	0 (0.0)	
Class C	0 (0.0)	0 (0.0)	
Kidney disorder (creatinine clearance)[a]	11 (5.1)	6 (4.7)	
Mild (50–80 mL/min)	3 (27.3)	5 (83.3)	
Moderate (30–50 mL/min)	3 (27.3)	1 (16.7)	
Severe (<30 mL/min)	1 (9.1)	1 (16.7)	
Hemodialysis required	4 (36.4)	0 (0.0)	
Allergic disorder	4 (1.9)	1 (0.8)	
Others	177 (81.9)	116 (90.6)	
Group by risk			0.320
High risk	187 (58.6)	118 (63.1)	
Low risk	132 (41.4)	69 (36.9)	
AAP treatment duration (mo)	6.6 (0.89–19.52)	4.9 (0.66–18.86)	0.004

Values are presented as mean±standard deviation, number (%), or median (range).
PSA, prostate-specific antigen; AAP, abiraterone acetate plus prednisolone.
[a]:Multiple answers are possible.

2. Treatment outcomes

A PSA reduction of greater than 50% was considered a PSA response following treatment. The PSA response in the pre-chemotherapy group was 61.8%, which was significantly higher than that in the post-chemotherapy group (39.0%, p<0.001) (Table 2). When PSA response was assessed in the risk-stratification model for both high-risk and low-risk patients, the pre-chemotherapy group achieved a higher PSA response than did the post-chemotherapy group. The median time to PSA progression was longer in the pre-chemotherapy group than in the post-chemotherapy group (5.00 vs. 2.93 mo, p=0.001) (Fig. 2A). Furthermore, the median time to rPFS was longer in the pre-chemotherapy group than in the post-chemotherapy group (11.84 vs. 9.17 mo, p=0.002) (Fig. 2B).

Risk factors for rPFS and PSA PFS were assessed using univariate and multivariate analyses, and post-chemotherapy status was associated with earlier radiologic and PSA progression compared with pre-chemotherapy status. In con-

Table 2. The outcome of PSA response

PSA response	Pre-chemotherapy (n=319)	Post-chemotherapy (n=187)	p-value
PSA response at any time			
PSA reduction ≥50%	197 (61.8)	73 (39.0)	<0.001
PSA response by risk			
High risk	187	118	
PSA reduction ≥50%	115 (61.5)	41 (34.8)	<0.001
Low risk	132	69	
PSA reduction ≥50%	82 (62.1)	32 (46.4)	0.032

Values are presented as number (%) or number only.
PSA, prostate-specific antigen.

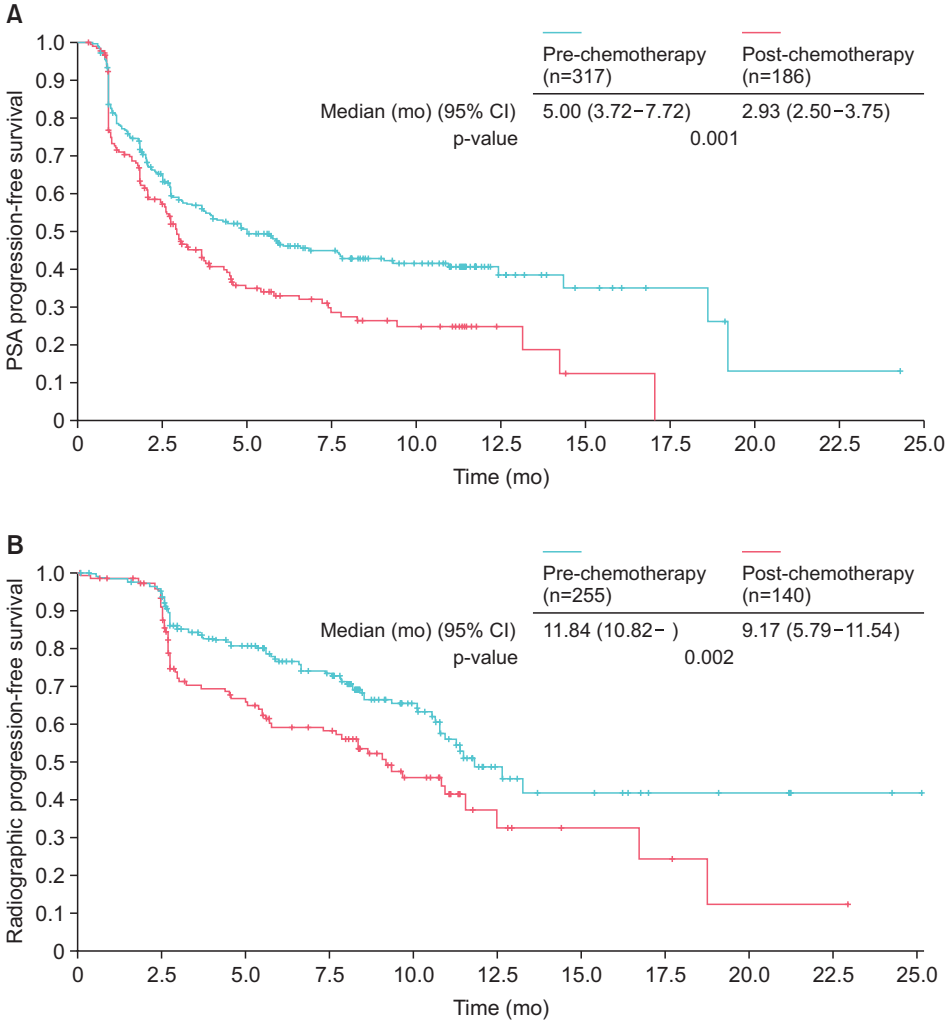

Fig. 2. Kaplan–Meier curves for prostate-specific antigen (PSA) progression and radiographic progression-free survival (rPFS). Kaplan–Meier curves for time to PSA progression and rPFS for pre-chemotherapy vs. post-chemotherapy patients. Pre-chemotherapy (blue; n=317) and post-chemotherapy (red; n=186) survival data are plotted in (A). Median PSA progression (mo) and 95% confidence intervals (CIs) are included (p=0.001). Pre-chemotherapy (blue; n=255) and post-chemotherapy (red; n=140) survival data are plotted in (B). Median rPFS (mo) and 95% CI are included (p=0.002).

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trast, age at enrollment, age at diagnosis, disease duration, risk stratification, definitive treatment, and comorbidities were not significant factors for disease progression during AAP treatment. Notably, baseline PSA over the median value was associated with early PSA progression, but not with radiologic progression (Table 3). In the multivariate analysis, post-chemotherapy status was the only significant factor associated with radiologic progression (hazard ratio [HR] 1.66, 95% confidence interval [CI] 1.18–2.33, p=0.004) and PSA progression (HR 1.39, 95% CI 1.09–1.77, p=0.008) (Table 4).

3. Adverse drug reactions

Adverse drug reactions were reported in 27 cases (8.46%) in the pre-chemotherapy group and 19 cases (10.16%) in the post-chemotherapy group. Specifically, increased levels of alanine aminotransferase and aspartate aminotransferase were reported in two and one patient, respectively, from the pre-chemotherapy group but did not lead to drug discontinuation. Peripheral edema was reported in one patient (0.31%) in the pre-chemotherapy group and in two patients (1.07%) in the post-chemotherapy group. Hypokalemia and hypertension were reported but were assessed to not be related to abiraterone. Rhabdomyolysis and thrombocytopenia were

Table 3. Univariate analyses of PSA PFS and rPFS

Variable	rPFS	p-value	PSA PFS	p-value
Chemotherapy		0.002		0.001
Pre	11.8±0.05 (10.82–)		5.0±0.03 (3.72–7.73)	
Post	9.2±0.05 (5.79–11.54)		2.9±0.04 (2.50–3.75)	
Age (y)		0.329		0.324
<75	11.5±0.06 (10.13–)		3.2±0.03 (2.76–4.44)	
≥75	11.3±0.05 (9.11–13.32)		5.0±0.04 (3.68–7.23)	
Age at diagnosis (y)		0.721		0.445
<Median (69)	10.9±0.05 (9.11–16.77)		4.3±0.03 (2.99–5.79)	
≥Median (69)	11.5±0.05 (10.16–)		3.7±0.03 (2.76–5.72)	
Disease duration (y)		0.063		0.208
<Median (3.16)	10.7±0.05 (8.52–12.53)		3.7±0.03 (2.76–4.83)	
≥Median (3.16)	11.8±0.06 (10.82–)		4.3±0.03 (2.99–7.40)	
Risk		0.018		0.450
Low	12.5±0.08 (11.51–)		4.8±0.04 (2.99–7.66)	
High	10.6±0.04 (8.55–11.44)		3.7±0.03 (2.76–4.60)	
Baseline PSA (ng/mL)		0.154		<0.001
<Median (33.97)	11.8±0.05 (10.65–)		9.3±0.04 (5.72–14.37)	
≥Median (33.97)	10.8±0.05 (9.17–12.53)		2.2±0.03 (1.94–2.76)	
Definitive treatment		0.114		0.958
Definitive treatment	10.8±0.06 (8.22–16.77)		3.9±0.03 (0.93–5.42)	
Non-definitive treatment	11.5±0.05 (10.65–13.32)		3.9±0.04 (2.76–5.79)	
Comorbidity		0.078		0.076
Yes	11.5±0.05 (10.16–18.77)		4.1±0.03 (3.12–5.79)	
No	10.9±0.06 (7.73–11.84)		3.2±0.04 (2.53–4.90)	

Values are presented as median±standard error (95% confidence interval).
PSA PFS, prostate-specific antigen progression-free survival; rPFS, radiologic progression-free survival.

Table 4. Multivariate analyses of PSA PFS and rPFS

Variable	rPFS		PSA PFS	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (≥75 vs. <75 y)	0.92 (0.65–1.31)	0.655	0.88 (0.69–1.12)	0.285
Chemotherapy (post vs. pre)	1.66 (1.18–2.33)	0.004	1.39 (1.09–1.77)	0.008
Risk (high vs. low)	1.49 (1.04–2.14)	0.029	1.05 (0.83–1.34)	0.678
Baseline PSA (≥33.97 vs. <33.97 ng/mL)	1.18 (0.84–1.65)	0.344	2.15 (1.68–2.75)	<0.001
Comorbidity (yes vs. no)	0.69 (0.49–0.98)	0.037	0.81 (0.63–1.03)	0.087

PSA PFS, prostate-specific antigen progression-free survival; rPFS, radiologic progression-free survival; HR, hazard ratio; CI, confidence interval.

not reported in the study. Serious adverse drug reactions such as pyrexia, fatigue, confusion, and diabetes mellitus were reported in four patients: two each in the pre- and post-chemotherapy groups (Supplementary Table 1). Adverse events led to permanent discontinuation in 9 patients (2.82%) in the pre-chemotherapy group and 17 patients (9.09%) in the post-chemotherapy group.

DISCUSSION

This study reports that use of AAP plus ADT before the administration of chemotherapy was more effective than post-chemotherapy use in suppressing the disease burden, as reflected by the PSA response. Furthermore, pre-chemotherapy treatment with AAP significantly delayed PSA PFS and rPFS compared with post-chemotherapy treatment with AAP. In addition, drug-related adverse effects were more frequent after post-chemotherapy use of AAP. The disease burden in the post-chemotherapy group tended to be higher with an increased number of bone metastases sites and higher PSA levels, which might have affected the therapeutic response to AAP. However, risk stratification showed a similar proportion of high- and low-risk patients in each group. Our findings varied, to an extent, from those of a previous study by Shameem et al., [14] who reported that pre-chemotherapy use of AAP did not delay PSA PFS or overall survival compared with post-chemotherapy use. However, those authors also reported that pre-chemotherapy AAP prolonged rPFS, and enhanced the objective response rate and PSA response rate, which was consistent with the present study findings.

In another study, Koroki et al. [15] evaluated the efficacy of AAP between chemotherapy-naïve and chemotherapy-administered groups. PSA response rate, defined by a 50% reduction from baseline, was higher in the chemotherapy-naïve group than in the chemotherapy-experienced group. The PSA response rate in the chemotherapy-naïve group was 34.8%, which is less than the 61.8% response rate observed in our study. Furthermore, overall survival was compared between the two groups, which can be halted by the lead time bias derived from longer disease duration in the chemotherapy-experienced group.

The limitation of the present study is that non-randomized modeling resulted in a higher tumor burden in the post-chemotherapy group. However, treatment response and adverse effects were reported and recorded prospectively through multiple centers, which reflects real-world practice and treatment results.

CONCLUSIONS

In conclusion, early treatment of mCRPC with AAP before chemotherapy induces a better treatment response, providing a higher PSA response rate and delayed disease progression compared with post-chemotherapy AAP treatment.

CONFLICTS OF INTEREST

SEY and SYK are employees of Janssen Korea Ltd. SEY was involved in study design, interpretation, funding, administrative support, and study supervision. SYK was involved in the statistical analysis and interpretation of the data. TWK declares participation in a Data Safety Monitoring Board or Advisory Board at Janssen. The remaining authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

Research conception and design: Seung-hwan Jeong, Sang Eun Yeon, and Cheol Kwak. Data acquisition: all authors. Statistical analysis: Su Youn Kim. Data analysis and interpretation: all authors. Drafting of the manuscript: Seung-hwan Jeong. Critical revision of the manuscript: Seung-hwan Jeong, Sang Eun Yeon, and Cheol Kwak. Obtaining funding: Sang Eun Yeon. Administrative, technical, or material support: Sang Eun Yeon and Cheol Kwak. Supervision: Seung-hwan Jeong, Sang Eun Yeon, and Cheol Kwak. Approval of the final manuscript: all authors.

SUPPLEMENTARY MATERIAL

Supplementary material can be found via https://doi.org/10.4111/icu.20230128.

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