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Prognostic significance of antihypertensive agents in men with castration-resistant prostate cancer

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Abstract

Purpose: Comorbidity with hypertension (HTN) may affect the outcome of castration-resistant prostate cancer (CRPC). In this study, we evaluated the prognostic impact of antihypertensive agents in patients with CRPC treated with androgen receptor axis-targeting (ARAT) agents or docetaxel chemotherapy.

Patients and methods: This study included 156 Japanese men with CRPC who were treated with ARAT agents ($n = 85$) or docetaxel ($n = 71$) at our hospital between 2008 and 2017. Associations between clinicopathological factors, HTN status, progression-free survival (PFS) and overall survival (OS) were evaluated by univariate and multivariate analysis.

Results: When adjusted for age, prostate-specific antigen levels at pretreatment, Gleason score, and clinical M-stage, comorbid HTN was significantly associated with better OS (hazards ratio, 95% confidence interval: 0.41, 0.21−0.77; $P = 0.0051$), but not with PFS (hazards ratio, 95% confidence interval: 0.64, 0.38−1.11; $P = 0.11$) in patients treated with ARAT agent. However, HTN was not associated with PFS or OS for patients treated with docetaxel.

Conclusions: Use of antihypertensive agents has prognostic significance for patients with CRPC treated with ARAT agent, but not docetaxel.

Keywords: Abiraterone; Castration-resistant prostate cancer; Docetaxel; Enzalutamide; Hypertension

1. Introduction

Androgen-deprivation therapy (ADT), alone or in combination with docetaxel or abiraterone, is currently the standard therapy for metastatic hormone-sensitive prostate cancer [1,2]. However, the majority of patients with this disease progress to castration-resistant prostate cancer (CRPC), even after consecutive courses of ADT. Current CRPC treatments include taxane chemotherapies (e.g., docetaxel and cabazitaxel), radium-223, novel androgen receptor axis-targeting (ARAT) agents such as enzalutamide and apalutamide, and the CYP17 inhibitor abiraterone [3,4] All of these treatments have shown several benefits, including prolonger survival, in clinical trials of patients with CRPC [3,4]. Thus, several therapeutic options are available for CRPC, highlighting the need to identify biomarkers that enable selection of a suitable therapy for each patient.

Several biomarkers have been suggested to predict a positive response to ARAT agents and taxane chemotherapies; these include the duration of response to primary ADT [5,6]; expression of the androgen receptor (AR) splice variant; and aberrations in the *AR* gene, DNA repair genes, and tumor-suppressor genes [7,8]. Hypertension (HTN) is a known risk factor for prostate cancer, albeit modest [9]. Conversely, HTN can itself be induced by prostate cancer treatments, such as the ARAT agents enzalutamide and abiraterone [10]. More recently, we reported the surprising

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finding that comorbidity with HTN was significantly associated with better prognosis in Japanese men treated with primary ADT for prostate cancer [11]. Moreover, several antihypertensive agents have been suggested to affect the incidence and outcome of prostate cancer [12,13]. Accordingly, use of antihypertensive agents may affect therapeutic outcome in CRPC. However, the prognostic significance for CRPC of HTN itself and medication for HTN remains scarcely revealed. Therefore, in this study, we examined the prognostic significance of medication for HTN in Japanese men receiving ARAT agents or docetaxel chemotherapy for CRPC.

2. Materials and methods

2.1. Patients

This study retrospectively enrolled 156 Japanese men with CRPC who were treated with ARAT agents ($n = 85$) or docetaxel ($n = 71$) at Kyushu University Hospital (Fukuoka, Japan) between 2008 and 2017. In the cohort of ARAT agents, patients treated with enzalutamide or abiraterone as first-line ARAT agents were included. Only patients with available information on comorbidity with hypertension were included. We excluded (1) patients with ethnicities other than Japanese, (2) patients who had been treated in clinical trials, (3) (for the ARAT agent cohort) patients treated previously for prostate cancer with apalutamide or TAK-700, and (4) (for the docetaxel cohort) patients treated previously for prostate cancer with an intravenous chemotherapeutic agent. This study was approved by the institutional review board of Kyushu University.

All patients were histopathologically diagnosed with adenocarcinoma of the prostate. Clinical staging was determined by the unified TNM criteria, based on the results of digital rectal examinations, transrectal ultrasound, magnetic resonance imaging, computed tomography, and bone scans [14]. Comorbidities with hypertension, dyslipidemia, and diabetes mellitus were defined as regular use of drugs for the corresponding disorders. Chronic kidney disease was defined as glomerular filtration rate of <60 ml/min. Comorbidity with cardiovascular disease was defined as past history in medical chart. Those comorbidities were determined at initiation of an ARAT agent or docetaxel for CRPC.

2.2. Treatments and outcomes

All patients were treated with an ARAT agent or docetaxel concurrent with either surgical castration or medical castration using a luteinizing hormone-releasing hormone agonist/antagonist (goserelin acetate, leuprorelin acetate, or degarelix acetate). The ARAT agents abiraterone and enzalutamide were administered at 1000 mg/day and 160 mg/day, respectively [15,16]. Docetaxel was administered at 70 to 75 mg/m^2 once every 3 or 4 weeks based on the schedule reported in the TAX 327 study [17]. Prednisone (5 mg) was generally administered twice daily to patients treated with abiraterone or docetaxel. The precise dose and scheduling of therapeutic agents were modified for each patient according to the severity of adverse events. Progression was defined as an increase in prostate-specific antigen (PSA) levels of >2ng/ml with a 25% increase over the nadir, or radiographic progression, which was defined as the appearance of 2 new lesions or the progression of one or more known lesions (as classified by the Response Evaluation Criteria in Solid Tumors) [18]. Progression and all-cause mortality were defined as an event in the analyses of progression-free survival (PFS) and overall survival (OS), respectively. The duration from initiation of an ARAT agent or docetaxel for CRPC to the earliest event or the censored date was calculated for analyses. Patients with no events were censored at the last follow-up visit.

2.3. Statistical analysis

All statistical analyses were performed using JMP13 software (SAS Institute, Cary, NC). Continuous and categorical data were analyzed by Wilcoxon's rank sum and Pearson's chi square tests, respectively. Survival analyses were conducted by the Kaplan-Meier method with Wilcoxon's test. The Cox proportional hazards model was used to estimate hazard ratios (HRs). All P values were 2-sided, and $P < 0.05$ was considered significant.

3. Results

3.1. Prognostic value of HTN in patients treated with ARAT agents

This study included 85 patients who were treated with abiraterone ($n = 29$) or enzalutamide ($n = 56$) as first-line ARAT agents. The median follow-up time was 13.6 months (interquartile range [IQR]: 7.1−24.4 months); during this time, 64 men (75.3%) experienced disease progression and 45 (52.9%) and 1 (1.2%) died from prostate cancer and cholangiocarcinoma, respectively. The median PFS and OS times were 5.1 months (IQR, 1.9−15.9 months) and 20.6 months (IQR, 7.7 months—not reached), respectively. Most patients had high PSA levels, high Gleason scores, and advanced M-stage at diagnosis and/or pretreatment (Table 1). Of the 85 men included, 41 (48.2%) were diagnosed with concurrent HTN. There were not significant differences in the clinicopathological characteristics of patients with and without HTN (Table 1).

The prognostic significance of clinicopathological features for PFS and OS were evaluated by univariate and multivariate analysis. Only M-stage was identified as a significant prognostic factor for PFS in univariate analysis (Table 2). Patients with HTN showed a trend towards better PFS, but it did not reach the level of statistical significance in either univariate analysis (hazards ratio [HR], 95% confidence interval [CI]: 0.66, 0.40−1.09; $P = 0.10$) (Fig. 1A,

Table 1
Clinicopathological characteristics of patients treated with first-line ARAT agents stratified by hypertension status

Variables	All ($n = 85$)	Absence of HTN ($n = 44$)	Presnece of HTN ($n = 41$)	P value
Median age at pretreatment, years (IQR)		72 (66–78)	75 (71–82)	0.075
Median PSA at diagnosis, ng/ml (IQR)	63.6 (15.5–238.6)	63.6 (15.6–407.0)	62.0 (13.1–222.3)	0.26
Biopsy Gleason score, *n* (%)				
<8	18 (22.0%)	11 (26.2%)	7 (17.5%)	
≥8	64 (78.0%)	31 (73.8%)	33 (82.5%)	0.34
NA	3	2	1	
Median PSA at pretreatment, ng/ml (IQR)	13.3 (4.8–29.0)	14.4 (6.9–41.2)	11.6 (4.1–23.1)	0.057
Clinical M-stage at pretreatment, *n* (%)				
M0	15 (17.6%)	7 (15.9%)	8 (19.5%)	
M1a	4 (4.7%)	3 (6.8%)	1 (2.4%)	
M1b	61 (71.8%)	30 (68.2%)	31 (75.6%)	
M1c	5 (5.9%)	4 (9.1%)	1 (2.4%)	0.40
First-line hormonal therapy, *n* (%)				
Combined androgen blockade	70 (82.4%)	37 (84.1%)	33 (80.5%)	
Castration	8 (9.4%)	2 (4.5%)	6 (14.6%)	
Antiandrogen monotherapy	7 (8.2%)	5 (11.4%)	2 (4.9%)	0.17
Time to CRPC from hormone therapy, months (IQR)	18.9 (10.0–43.3)	16.1 (9.3–39.5)	20.9 (10.0–51.8)	0.47
Prior radical therapy, *n* (%)				
None	59 (69.4%)	32 (72.7%)	27 (65.9%)	
Radical prostatectormy	13 (15.3%)	6 (13.6%)	7 (17.1%)	
Radiotherapy	13 (15.3%)	6 (13.6%)	7 (17.1%)	0.79

IQR = interquartile range; NA = not available; PS = performance status.

Table 2) or multivariate analysis after adjustment for age, PSA levels at diagnosis, Gleason score, and clinical stage (HR, 95% CI: 0.60, 0.34–1.08; $P = 0.090$) (Table 2).

Notably, we found that HTN was significantly associated with better OS in both univariate analysis (HR, 95% CI: 0.45, 0.24–0.81; $P = 0.0080$) (Fig. 1B, Table 2) and multivariate analysis (HR, 95% CI: 0.41, 0.21–0.77; $P = 0.0051$) when adjusted for age, PSA levels at pretreatment, Gleason score, and clinical M-stage (Supplementary Table 1).

Because HTN is known to coexist with other disorders such as dyslipidemia, diabetes mellitus, chronic kidney disease, and cardiovascular disease, we investigated the prognostic impact of those disorders. In the cohort of ARAT agents, 25 men (29.4%), 20 (23.5%), 27 (31.8%), and 23 (27.1%) were comorbid with dyslipidemia, diabetes mellitus, chronic kidney disease, and cardiovascular disease, respectively. However, comorbidities with dyslipidemia, diabetes mellitus, chronic kidney disease, and

Table 2
Associations between clinicopathological parameters and prognosis in patients treated with first-line ARAT agent

Variable	Progression-free survival			Overall survival		
	HR	95% CI	P value	HR	95% CI	P value
Age at pretreatment (range)	0.78	0.20–3.16	0.73	1.01	0.17–5.92	0.99
PSA at diagnosis (range)	1.13	0.17–4.72	0.89	1.41	0.21–5.72	0.69
Biopsy Gleason score						
<8	ref	–	–	ref	–	–
≥8	1.19	0.66–2.30	0.58	0.96	0.51–1.94	0.90
PSA at pretreatment (range)	2.44	0.19–10.48	0.41	3.17	0.25–13.64	0.30
Clinical M-stage						
M0	ref	–	–	ref	–	–
M1a	2.28	0.48–8.68	0.27	0.64	0.033–4.35	0.68
M1b	3.06	1.41–7.99	0.0031*	2.38	0.95–7.98	0.065
M1c	4.28	1.22–14.37	0.025*	8.83	2.29–36.34	0.0022*
Comorbidity of hypertension						
Absence	ref	–	–	ref	–	–
Presence	0.66	0.40–1.09	0.10	0.45	0.24–0.81	0.0080*

HR = hazards ratio; CI = confidence interval; PSA = prostate-specific antigen; PS = performance status.
* Statistically significant.

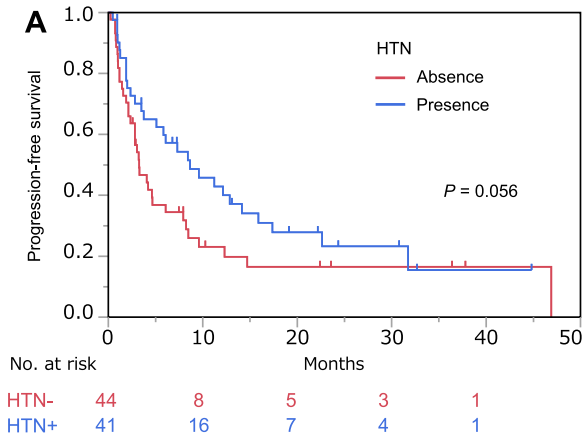

Fig. 1. Survival curves of men with CRPC treated with ARAT agents according to HTN status. Progression-free survival (A) and overall survival (B) of 85 patients stratified by HTN comorbidity.

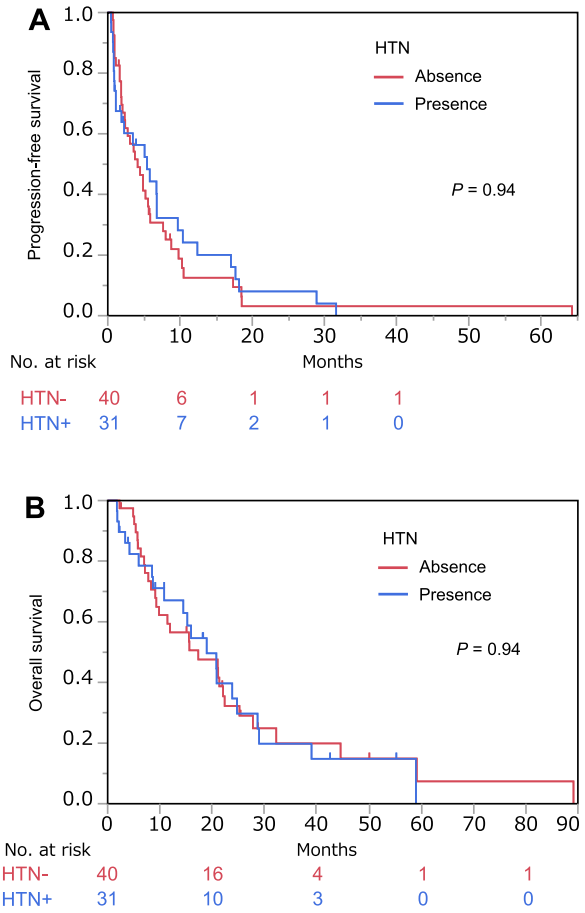

Fig. 2. Survival curves of men with CRPC treated with docetaxel chemotherapy according to HTN status. Progression-free survival (A) and overall survival (B) of 71 patients stratified by HTN comorbidity.

cardiovascular disease were not associated with prognoses in patients treated with ARAT agents (data not shown).

3.2. *Prognostic value of HTN in docetaxel-treated patients*

Next, we performed the same analyses on the 71 patients who were treated with docetaxel as first-line chemotherapy. The median follow-up was 14.4 months (IQR: 5.8−23.8 months); during this time, 64 men (90.1%) experienced disease progression and 50 (70.4%) and 1 (1.4%) died from prostate cancer and suicide, respectively. The median PFS and OS times were 4.9 months (IQR, 1.6−9.7 months) and 18.9 months (IQR, 8.3−28.7 months), respectively. Most patients presented with high Gleason scores at diagnosis and with high PSA levels at diagnosis and pre-treatment (Supplementary Table 2). All patients had distant metastases before treatment (Supplementary Table 2) and 31 men (43.7%) were diagnosed with HTN. The clinicopathological characteristics of men with and without HTN were comparable, except that a Gleason score of ≥8 was more common among the men with HTN (Supplementary Table 2).

Comorbid HTN was not significantly associated with PFS or OS in either univariate or multivariate analyses. Thus, the HR (95% CI) for PFS, and OS in univariate analysis were 0.92 (0.55−1.52; $P = 0.76$) (Fig. 2A) and 1.06, (0.59−1.86; $P = 0.84$) (Fig. 2B), respectively, and in multivariate analysis were 0.85 (0.46−1.53; $P = 0.60$) and 1.00 (0.51−1.92; $P = 1.00$), respectively, after adjustment for age, PSA levels at diagnosis, Gleason score, and clinical stage (Supplementary Table 4).

In the cohort of docetaxel, 12 men (16.9%), 13 (18.3%), 18 (25.4%), and 15 (21.1%) were comorbid with dyslipidemia, diabetes mellitus, chronic kidney disease, and cardiovascular disease, respectively. However, comorbidities with dyslipidemia, diabetes mellitus, chronic kidney disease, and cardiovascular disease were not associated with prognoses in patients treated with docetaxel (data not shown).

4. Discussion

The results of this study suggest that comorbidity with HTN is a prognostic factor for OS in patients treated with first-line ARAT agents (abiraterone or enzalutamide). We

previously showed that men with HTN had a better prognosis than men without HTN after treatment with primary ADT for metastatic prostate cancer [11]. In a preclinical study, we found that activated mineralocorticoid receptor (MR) signaling was associated with vulnerability to antiandrogen therapy [19]. Mineralocorticoids have been shown to inhibit AR activity [20], while MR antagonists directly activate AR [21]. Thus, molecular effect of MR on AR might be involved in sensitivity to antiandrogen therapy. Thus, it is possible that the better therapeutic outcome of men with HTN after treatment with ARAT agents in our study is linked to enhanced MR signaling in men comorbid with HTN. However, other causes of HTN such as salt overload, obesity, psychiatric stress, cigarette smoking, and alcohol dinging may also be involved in prognostic significance of comorbidity with HTN in treatment with ARAT agents. Although functional mechanisms of anticancer effect differ between abiraterone and enzalutamide, both agents inhibit AR signaling similar to ADT. Then, prognostic significance of HTN is expected to be consistent between abiraterone and enzalutamide although the sample number in each ARAT agent is too small to perform robust analysis in this study. However, further investigation on this issue would be required in the future. The results of the present study are also consistent with those of Goyal et al., who found that HTN was not associated with prognosis in docetaxel-treated US residents with CRPC [22]. Taken together, these observations support the conclusion that HTN is significantly associated with survival in men treated with hormone therapy, including primary ADT and ARAT agents, but not with taxane chemotherapy.

Interestingly, several antihypertensive drugs have been found to affect the proliferation and survival of prostate cancer cells as well as the survival of prostate cancer patients. In a prospective cohort study of men with prostate cancer in the United Kingdom, the mortality rate of those taking angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers was lower than the men who were not taking medications [23]. This finding is supported by a preclinical study in a rat model of prostate cancer [24]. Because comorbidity with HTN was defined by regular intake of antihypertensive agents, antihypertensive drugs may influence the prognosis of prostate cancer patients with HTN who are treated with ARAT agents. However, the small sample number in this study did not allow us to analyze the prognostic value of specific antihypertensive drugs. In addition, because comorbidity with HTN was not prognostic in docetaxel chemotherapy, favorable effects of antihypertensive drugs might be specific for ARAT agents.

The present study has several limitations. The samples size was relatively small, and the study design was retrospective. Only Japanese were included in this study. The data on PSA level at diagnosis and Gleason score in a few patients is missing. The detailed data on intake of antihypertensive drugs and disease control are lacking. Comorbidity with HTN was defined only by regular intake of antihypertensive agents, and some cases may therefore have been overlooked. The accrual period of the docetaxel cohort was long, and included the period before novel therapies for CRPC were introduced (e.g., abiraterone acetate, enzalutamide, radium-233, and cabazitaxel). In addition, the competing risk of death by comorbid HTN may have affected the results; we believe this to be unlikely because the cause of death in this cohort was predominantly prostate cancer.

This study showed that use of antihypertensive agents has prognostic significance for men treated for prostate cancer with ARAT agents but not for those treated with docetaxel. This suggests that HTN could be a predictive marker for response to a particular therapy. However, further investigations in other ethnic groups will be required to verify these findings.

Conflict of interest

We declare no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2019.04.020.

References

[1] Shiota M, Eto M. Current status of primary pharmacotherapy and future perspectives toward upfront therapy for metastatic hormone-sensitive prostate cancer. Int J Urol 2016;23:360–9.
[2] Komura K, Sweeney CJ, Inamoto T, Ibuki N, Azuma H, Kantoff PW. Current treatment strategies for advanced prostate cancer. Int J Urol 2018;25:220–31.
[3] Fujimoto N. Novel agents for castration-resistant prostate cancer: early experience and beyond. Int J Urol 2016;23:114–21.
[4] Smith MR, Saad F, Chowdhury S, et al. Apalutamide treatment and metastasis-free survival in prostate cancer. N Engl J Med 2018;378:1408-8.
[5] Loriot Y, Eymard JC, Patrikidou A, et al. Prior long response to androgen deprivation predicts response to next-generation androgen receptor axis targeted drugs in castration resistant prostate cancer. Eur J Cancer 2015;51:1946–52.
[6] Huillard O, Albiges L, Eymard JC, et al. Efficacy of docetaxel chemotherapy in metastatic prostate cancer (mPC) patients (pts) experiencing early castration resistance (CR). In: ASCO Annual Meeting; 2013.abs#5075.
[7] Scher HI, Graf RP, Schreiber NA, et al. Assessment of the validity of nuclear-localized androgen receptor splice variant 7 in circulating tumor cells as a predictive biomarker for castration-resistant prostate cancer. JAMA Oncol 2018;4:1179–86.

[8] Annala M, Vandekerkhove G, Khalaf D, et al. Circulating tumor DNA genomics correlate with resistance to abiraterone and enzalutamide in prostate cancer. Cancer Discov 2018;8:444–57.
[9] Liang Z, Xie B, Li J, et al. Hypertension and risk of prostate cancer: a systematic review and meta-analysis. Sci Rep 2016;6:31358.
[10] Iacovelli R, Ciccarese C, Bria E, et al. The cardiovascular toxicity of abiraterone and enzalutamide in prostate cancer. Clin Genitourin Cancer 2018;16:e645–53.
[11] Shiota M, Fujimoto N, Imada K, et al. Prognostic impact of genetic polymorphism in mineralocorticoid receptor and comorbidity with hypertension in androgen-deprivation therapy. Front Oncol 2018;8:635.
[12] Cao L, Zhang S, Jia CM, et al. Antihypertensive drugs use and the risk of prostate cancer: a meta-analysis of 21 observational studies. BMC Urol 2018;18:17.
[13] Stopsack KH, Greenberg AJ, Mucci LA. Common medications and prostate cancer mortality: a review. World J Urol 2017;35:875–82.
[14] International Union Against Cancer: Urologic Tumors. Prostate. In: Sobin LH, Wittekind CH, eds. TNM classification of malignant tumors, 5th ed., New York: John Wiley & Sons; 1997:170–3.
[15] de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011;364:1995–2005.
[16] Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012;367:1187–97.
[17] Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004;351:1502–12.
[18] Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 2008;26:1148–59.
[19] Shiota M, Fujimoto N, Higashijima K, et al. Mineralocorticoid receptor signaling affects therapeutic effect of enzalutamide. Prostate 2018;78:1045–52.
[20] Kim W, Jones JO, Diamond M, et al. Inhibition of the androgen receptor by mineralocorticoids at levels physiologically achieved in serum in patients treated with abiraterone acetate. Prostate Cancer Prostatic Dis 2014;17:292–9.
[21] Richards J, Lim AC, Hay CW, et al. Interactions of abiraterone, eplerenone, and prednisolone with wild-type and mutant androgen receptor: a rationale for increasing abiraterone exposure or combining with MDV3100. Cancer Res 2012;72:2176–82.
[22] Goyal J, Pond GR, Galsky MD, et al. Association of the Charlson comorbidity index and hypertension with survival in men with metastatic castration-resistant prostate cancer. Urol Oncol 2014;32:36.e27-34.
[23] Cardwell CR, Mc Menamin ÚC, Hicks BM, Hughes C, Cantwell MM, Murray LJ. Drugs affecting the renin-angiotensin system and survival from cancer: a population based study of breast, colorectal and prostate cancer patient cohorts. BMC Med 2014;12:28.
[24] Takahashi S, Uemura H, Seeni A, et al. Therapeutic targeting of angiotensin II receptor type 1 to regulate androgen receptor in prostate cancer. Prostate 2012;72:1559–72.