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Therapeutic Effect of Ethinylestradiol in Castration-resistant Prostate Cancer

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Abstract. *Background/Aim: The best sequential treatment for castration-resistant prostate cancer (CRPC) remains unclear. This study evaluated the therapeutic effects of ethinylestradiol (EE) on CRPC. Patients and Methods: A total of 80 patients with CRPC, treated with 0.5-1.5 mg/day of EE, were retrospectively assessed. Results: The median duration from the initial treatment to the beginning of EE was 48.3 months. A decline in the prostate-specific antigen (PSA) from the baseline was noted in 60 patients (75%) and a >50% PSA decline in 27 patients (34%). The median time of PSA progression, overall survival, and cancer-specific survival after EE were 5.60 months, 24.00 months, and 27.93 months, respectively. Conclusion: EE administration for CRPC showed a relatively high PSA response regardless of timing of sequential treatment. The frequency of cardiovascular adverse events was not significantly high. EE administration is a potential treatment option for CRPC.*

Estrogen therapy has long been the treatment of choice for prostate cancer (PC). However, this gradually changed because of its involvement in cardiovascular toxicity, particularly thromboembolism, and due to the development of new therapeutic agents with a theoretically superior safety profile (1). The luteinizing hormone-releasing hormone (LH-RH) agonist has become the main first-line therapy agent for PC (2, 3). Androgen-deprivation therapy (ADT) using LH-RH is currently the most common treatment for locally advanced and metastatic PC; however, the development of resistance to ADT, known as castration-resistant PC (CRPC), is inevitable (4, 5). Several drugs have been developed and diversified in CRPC treatment strategies (4-8). CRPC is difficult to treat; hence, the preferred strategy for CRPC management would be an appropriate sequential treatment using these drugs. However, the best sequential treatment for CRPC remains unclear. Estrogen therapy is currently not used as the first-line therapy for PC due to the adverse events (AEs) it poses; however, its effectiveness in CRPC has been reported (9-11). Low-dose estrogens have been found to reduce the occurrence of thromboembolic complications, which is the primary AE of estrogen therapy, compared to the high-dose administration implemented in the past (11, 12).

Ethinylestradiol (EE) is an estrogen preparation that is inexpensive, available as an outpatient treatment, and relatively easy to use for the elderly. This study evaluated the treatment results of EE in CRPC patients at our hospital.

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Key Words: Ethinylestradiol, castration resistant prostate cancer, prostate-specific antigen, adverse event.

Patients and Methods

This study was conducted using the databases of the Kanazawa University Hospital with the approval from the institutional review board (approval number 3248-1). Data from 80 CRPC patients treated with EE at Kanazawa University Hospital from May 2005 to September 2018 were retrospectively analyzed. Patients were orally given 0.5-1.5 mg/day of EE. All patients had histologically confirmed prostate adenocarcinoma. If the physician detected i) increased PSA levels, ii) deteriorated state of PC, and iii) presence of AEs, either additional treatment was administered or EE was discontinued. The overall survival (OS), cancer-specific survival (CSS), and the PSA progression-free survival (PFS) after EE administration and predictors associated with PSA response were evaluated. The maximal PSA decline was based on the value obtained >4 weeks after treatment. The time to PSA progression was defined as the time PSA levels increased to 25% above the nadir, with PSA>2 ng/ml.

The OS, CSS, and PFS were estimated using the Kaplan-Meier method, and PSA decline predictors were analyzed using the univariate Cox proportional hazards regression model. Data analyses were done using the Statistical Package for the Social Sciences software for Windows (SPSS Inc., Chicago, IL, USA), and statistical significance was defined as having a p-Value<0.05.

Results

Table I summarizes the patient characteristics. Abiraterone and/or enzalutamide was given in 25 patients (31%) before EE and in 25 patients (31%) after EE administration. However, abiraterone and enzalutamide were not administered in 35 patients (44%). The median course of systemic therapy before EE administration was 3.6 lines, and the median duration from the initial treatment to the start of EE treatment was 48.3 months.

Figure 1 displays the maximum changes in PSA responses after EE treatment. A PSA decline from the baseline level was noted in 60 patients (75%). Moreover, 40 (50%) and 27 patients (34%) demonstrated a >30% PSA decline and a >50% PSA decline, respectively.

At the end of the follow-up period, 13 out of 80 patients (16.3%) were alive. Figure 2 presents the Kaplan–Meier curves on time to PSA progression, OS, and CSS. The median time to PSA progression after EE treatment was 5.60 months [95% Confidence Interval (CI)=3.12-8.08 months]; the median OS after EE was 24.00 months (95%CI=16.54-31.50 months); and the median CSS after EE was 27.93 months (95%CI=21.00-34.87 months).

EE was discontinued in six cases (8%) due to liver dysfunction in three cases (7, 28, and 29 days after start of treatment), systemic edema in one (33 days after start of treatment), pulmonary embolism in one (77 days after start of treatment), and heart failure in one (20 days after start of treatment). In addition, PSA response predictors were analyzed (Table II). In a univariate analysis, there are no factors predicting the PSA decrease rates of >0%, >30%, and >50%.

Table I. *Patient characteristics*.

	n (range or %)
Patient number	80
Median age at diagnosis	67 (46-86)
Median PSA (ng/ml) at diagnosis	111.1 (3.4-10000)
Median age at starting EE	71 (51-87)
Median PSA (ng/ml) at starting EE	35.9 (0.024-3096.8)
Median follow up (days) after starting EE	466 (36-3128)
Median administration (days) of EE	134 (7-721)
Gleason score at initial biopsy	
<7 or well differentiated	0 (0%)
7 or moderately differentiated	14 (18%)
>7 or poorly differentiated	61 (76%)
Unknown	5 (6%)
Metastatic sites at starting EE	
None	4 (5%)
Lymph node	44 (55%)
Bone	71 (89%)
Lung	4 (10%)
Liver	1 (1%)
Ureter	1 (1%)
Prior treatment	
Radical prostatectomy	5 (6%)
Brachytherapy	33 (40%)
Castration	82 (100%)
Bicaltamide	82 (100%)
Flutamide	70 (85%)
Chrolmadinone phosphate	10 (12%)
Estramustine phophate	48 (58%)
Docetaxel	17 (21%)
Enzaltamide	15 (18%)
Abiraterone	16 (20%)
Zoredronic acid	45 (55%)
Denosuzumab	5 (6%)
Cabazitaxel	5 (6%)
Dexamethasone	14 (17%)
Prednisolone	29 (35%)
Stontium	4 (5%)
Radium-223	9 (11%)
Tegafur uracil	7 (9%)
Tranilast	5 (6%)
Treatment after EE	
Docetaxel	34 (41%)
Enzaltamide	18 (21%)
Abiraterone	14 (17%)

PSA: Prostate specific antigen; EE: ethinylestradiol.

Discussion

Treatment strategies for CRPC vary. Several treatment options for CRPC, such as newly developed ADT agents (4, 5, 7, 8), anticancer chemotherapy (6), and radionuclide therapy (13), have been identified. Consequently, the frequency of EE use has drastically decreased. This study evaluated the efficacy and safety of EE treatment in CRPC. Two-thirds of our cohort manifested a PSA response and one-third a PSA decline over 50% after EE administration. No influential factors, such as treatment agents for PSA decline after EE administration, were shown in this study; hence, it would be unnecessary to consider treatment sequence in the case of EE use. In this study, EE discontinuation due to AE was noted in 8% of patients and discontinuation due to thrombosis in one case.

Based on results of past clinical trials, the current treatment options for CRPC include docetaxel, enzalutamide, and abiraterone. Enzalutamide, in a pre-docetaxel setting, has shown a median PSA PFS of 11.2 months (4) and in a post-docetaxel setting, a median PSA PFS of 8.3 months (7). Abiraterone has shown a median PSA PFS of 11.1 months in a pre-docetaxel setting (5) and a median PSA PFS of 8.5 months in a post-docetaxel setting (8). In their study in 2010, Izumi *et al*. reported that 70% of patients showed a >50% PSA decline, the median PSA PFS was 300 days, and the treatment effect of EE was comparable with docetaxel (14). In a recent report, Roviello *et al*. have indicated that low-dose EE (0.15 mg/day) can show a median PSA PFS of 9.4 months for chemo-naive metastatic CRPC (11), and Sciarra

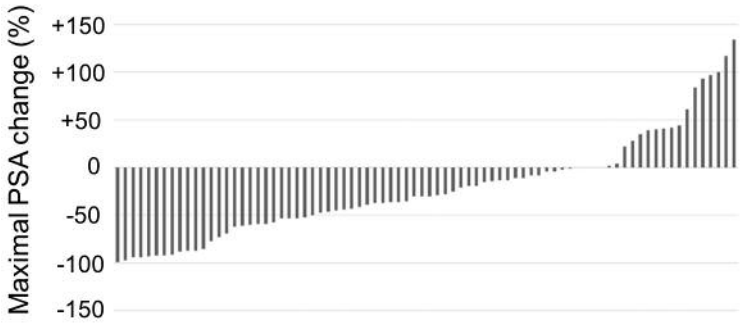
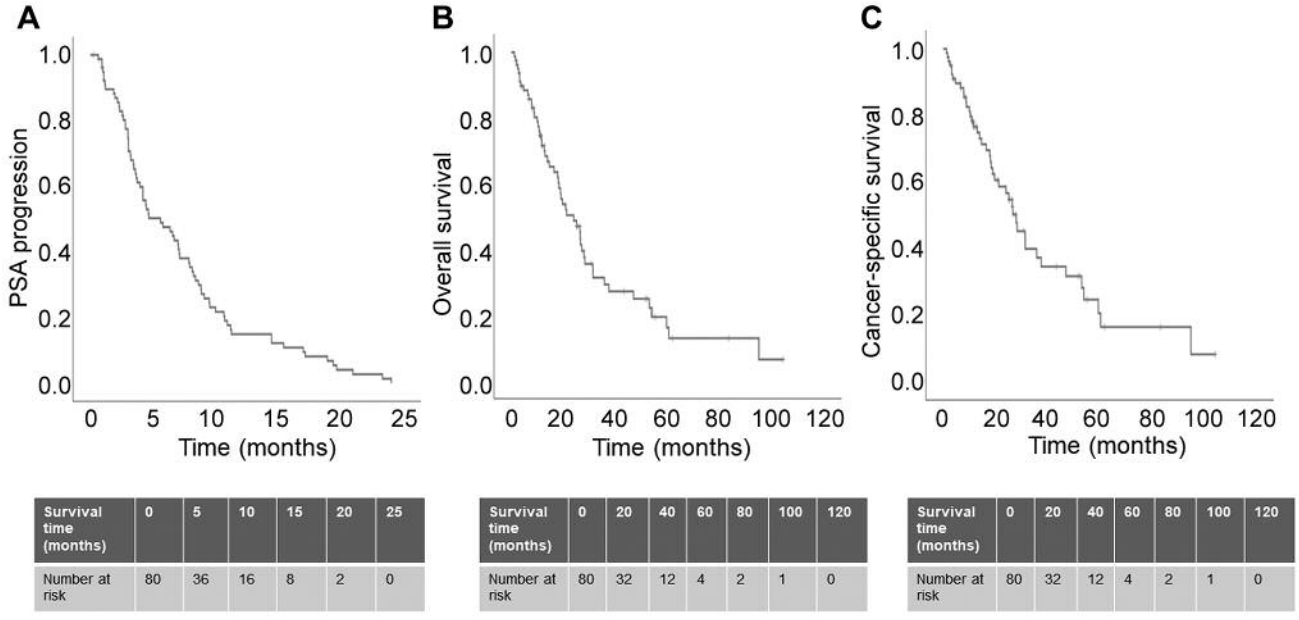


Figure 1. *Maximum changes in prostate-specific antigen (PSA) after starting ethinylestradiol shown by waterfall plots. A PSA decline from the baseline level was noted in 60 patients (75%); 40 (50%) and 27 patients (34%) demonstrated a >30% and >50% PSA decline, respectively. N: Number of patients.*



Survival time (months)	0	5	10	15	20	25
Number at risk	80	36	16	8	2	0

Survival time (months)	0	20	40	60	80	100	120
Number at risk	80	32	12	4	2	1	0

Survival time (months)	0	20	40	60	80	100	120
Number at risk	80	32	12	4	2	1	0

Figure 2. *Kaplan-Meier curves. (A) Shows time to prostate-specific antigen (PSA) progression, (B) overall survival, and (C) cancer-specific survival.*

et al. have reported that 1 mg/day of EE can show a median PSA PFS of 15.1 months for PC patients administered with at least 2 lines of ADT (10). The median PSA PFS of 5.6 months determined in this study was a short effective duration compared to that of the previous study (10,11). More treatment lines than used in our study (median=3.6) before EE administration, would affect the effective duration.

Several possible mechanisms for the effectiveness of estrogen in CRPC have been reported. Estrogen has been found to inhibit the hypothalamic-pituitary-testicular axis, and the negative feedback can inhibit testosterone production and decrease both dehydroepiandrosterone (DHEA) and DHEA sulphate from the adrenal gland (15). In a mouse PC model with androgen deprivation, estrogen has been observed to inhibit cancer progression (16). An experiment using human CRPC xenograft has revealed that estradiol suppresses CRPC progression (17). Moreover, estrogen has been shown to regulate tubulin levels, as well as tubulin stability, which is an important component of PC and a central target of taxane agents (18). In addition, estrogen has been detected as a potent inhibitor of telomerase, which is highly up-regulated in malignant cells (19), and an inducer of antiangiogenic effects, which inhibit angiogenesis necessary for tumor expansion, by inhibiting the growth and migration of vascular smooth muscle cells (20).

Table II. *Univariate logistic regression analysis for PSA decline after administration.*

	PSA<50%		PSA<30%		PSA<0%	
	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value
Age (1st visit), years	1.003 (0.951-1.059)	0.906	1.017 (0.966-1.071)	0.511	1.001 (0.943-1.063)	0.967
Initial PSA* (ng/ml)	1.000 (0.999-1.000)	0.513	1.000 (0.999-1.000)	0.208	1.000 (0.999-1.000)	0.182
N0M0	1 (Reference)		1 (Reference)		1 (Reference)	
N1M0	0.300 (0.028-3.250)	0.322	0.333 (0.046-2.431)	0.279	1.000 (0.134-7.451)	1
NxM1	0.789 (0.246-2.534)	0.691	0.667 (0.210-2.114)	0.491	1.917 (0.551-6.673)	0.307
Gleason score**						
7	1 (Reference)		1 (Reference)		1 (Reference)	
8	0.636 (0.155-2.613)	0.531	0.444 (0.106-1.867)	0.268	0.955 (0.176-5.186)	0.957
9~10	0.323 (0.091-1.145)	0.08	0.435 (0.124-1.525)	0.193	0.744 (0.174-3.176)	0.689
Local therapy						
Negative (–)	1 (Reference)		1 (Reference)		1 (Reference)	
Positive (+)	0.429 (0.163-1.129)	0.277	1.056 (0.436-2.555)	0.905	0.736 (0.262-2.071)	0.562
Docetaxel administration before EE						
Negative (–)	1 (Reference)		1 (Reference)		1 (Reference)	
Positive (+)	0.580 (0.167-2.008)	0.39	1.327 (0.440-4.004)	0.615	1.475 (0.372-5.850)	0.58
Abi and/or Enz administration before EE						
Negative (–)	1 (Reference)		1 (Reference)		1 (Reference)	
Positive (+)	0.496 (0.170-1.445)	0.199	0.857 (0.332-2.214)	0.75	1.004 (0.331-3.046)	0.994

PSA: Prostate specific antigen; EE: ethynilestradiol; Abi: abiraterone; Enz: enzalutamide; HR: hazard ratio. *Initial PSA was missing in 2 cases. **Gleason score was missing in 6 cases.

Although therapeutic agents for CRPC have been reported, the main sequential therapy for CRPC to lengthen OS has not been determined. Hakariya *et al*. have reported an attenuation effect of enzalutamide for PSA response after EE in a pre-docetaxel setting (9). In this study, the predictors of PSA response were not shown, and the use of docetaxel, abiraterone, or enzalutamide prior to EE administration had no effect on the PSA response rate. Therefore, EE may have a certain therapeutic effect regardless of the timing of the sequential therapy for CRPC. In addition, Onishi *et al*. have observed a positive PSA response in metastatic CRPC in one-third of their patients who received re-EE after disease progression on prior EE and other therapy (21). EE administration would be effective for CRPC in any steps; therefore, EE should be considered as one of the treatment options in sequential therapy for CRPC.

The occurrence of AEs is the reason why estrogen use in PC has been declined. Henriksson *et al*. report that 25% of the patients who underwent estrogen therapy manifested cardiovascular complications during the initial treatment year compared to none in the orchiectomy group (22). Historically, diethylstilbestrol (DES) has probably been the most commonly used estrogen in PC. When administered daily at 3.0-5.0 mg it has been associated with severe cardiovascular toxicity (2,23). Dose reduction or alteration of the administration route have decreased AEs of DES. Bailar *et al*. have shown that in the prevention of death from PC without a concomitant association with increased frequency of cardiovascular mortality, 1 mg of DES was as effective as 5 mg of DES and was significantly more effective compared to the 0.2 mg dose or placebo (24). Estrogen administered orally is absorbed by the gastrointestinal tract and transported to the liver through the hepatic portal vein. The estrogen in the liver activates the blood coagulation system, resulting in a high risk for venous thromboembolism (25). Transdermal estradiol therapy using infused patches has been reported to affect the blood coagulation system only slightly, because the transdermal estrogen is distributed throughout the entire body before its passage to the liver (26). Recent major studies on DES use in CRPC reported that the ideal dose for DES to be effective and induce fewer side effects is 1-2 mg/day (12). However, Sciarra *et al*. have indicated that oral EE at a daily dose of 1 mg causes toxicity, warranting treatment cessation mainly due to thromboembolism (10). Furthermore, Roviello *et al*. have stated that a daily EE dose of 0.15 mg is effective for CRPC, with a cardiac event observed in only 1 out of 32 cases (9); hence, a low-dose EE administration might be an effective and safe treatment for CRPC. The ethnic difference of the crisis rate of deep vein thrombosis caused by estrogen has been reported with a lower frequency in Asians, including Japanese, compared to Westerners (27). In this study, EE was administered at a dose of 0.5-1.5 mg/day, and from 80 cases it was discontinued in only two, due to cardiovascular events, one pulmonary embolism and one cardiac failure. Estrogen administration is responsible for many AEs; however, it might also provide some advantages for patients. Miller JI *et al*. have shown that men that went under orchiectomy for advanced PC

experienced significant improvement from hot flushes with low-dose DES (28). Langley *et al*. have reported that transdermal estradiol produces castration levels of testosterone and reduces bone mineral density loss usually observed after a long-term ADT (29).

This study had a few limitations. A retrospective method was applied, and the timing of EE administration depended on the doctors in charge; thus, it was difficult to evaluate whether EE administration contributed in the increase of the OS. The treatment effect was evaluated only by measuring PSA, while no imaging methods were performed.

In conclusion, EE administration for CRPC showed a relatively high PSA response regardless of the timing during the sequential treatment. Cardiovascular AEs caused by EE administration were considered; however, their frequency was not significantly high. Thus, EE administration is a potential treatment option for CRPC.

Conflicts of Interest

All Authors declare that they have no conflicts of interest with regard to this study.

Authors' Contributions

TN, MI, HI and HY collected the data. TN, MI and SK drafted the manuscript. YK, SK, KS and KI analyzed the data. YK, HI, HY, TN, KS, KI and AM revised the manuscript. YK, TN and AM conceived and revised the study. All authors read and approved the final manuscript

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