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# Low-Dose Oral Ethinylestradiol With Concomitant Low-Dose Acetylsalicylic Acid for Advanced Castrate-Resistant Prostate Cancer

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## Abstract

**The aim of the present study was to evaluate the activity and tolerability of low-dose oral ethinylestradiol and luteinizing hormone-releasing hormone analogue with concomitant low-dose acetylsalicylic acid for advanced castrate-resistant prostate cancer. Of the 32 enrolled patients, a prostate-specific antigen response was observed in 19 (59.3%). The median progression-free survival was 9.4 months. Treatment was generally well tolerated, and no grade 3/4 toxicity was observed.**

**Background:** The aim of the present study was to evaluate the activity and tolerability of low-dose oral ethinylestradiol (EE) and luteinizing hormone-releasing hormone analogue with concomitant low-dose acetylsalicylic acid (ASA) as a thromboprophylactic agent for advanced castrate-resistant prostate cancer (CRPC). **Patients and Methods:** The patients received an EE dose of 150 μg daily (50 μg 3 times daily) and an ASA dose of 100 mg once daily. The primary endpoint was the prostate-specific antigen response. **Results:** A total of 32 patients were enrolled. A PSA response was observed in 19 patients (59.3%; 95% confidence interval [CI], 41%-76%). The median progression-free survival was 9.4 months (95% CI, 6.5-14.1 months). The treatment was generally well tolerated and no grade 3-4 toxicity was observed. Only 1 patient interrupted EE because of a cardiac event and 1 patient experienced grade 2 nausea and vomiting. No major bleeding occurred. **Conclusion:** Low-dose EE with concomitant low-dose ASA is safe, showing potential activity in patients with advanced CRPC, and should be investigated further.

**Keywords:** Castration-resistant prostate cancer, Estrogens, Hormonal therapy

## Introduction

Prostate cancer is the second leading cause of cancer-related death in men in western countries. Androgen-deprivation, either from surgery (bilateral orchiectomy) or administration of gonadotropin-releasing hormone agonists or antagonists therapy, is considered the first approach for advanced and metastatic disease.[1] However, most of the patients develop progression toward castration-resistant prostate cancer (CRPC). In this setting, docetaxel plus prednisone was the first therapeutic approach able to improve survival compared with older regimens.[2,3] Recently, new hormonal agents have been added to the standard chemotherapy agents, including abiraterone acetate, an irreversible P450c17 (CYP17) inhibitor that blocks androgen biosynthesis, and enzalutamide, a second-generation androgen receptor antagonist.[4] The benefit of these drugs in the CRPC setting has been widely demonstrated.[4]

Oral ethinylestradiol (EE) previously demonstrated preclinical and clinical activity in prostate cancer. Several studies have reported that estrogens have a direct toxic effect on prostate cancer cells by induction of apoptosis, in addition to indirect antitumor activity related to the downregulation of the serum testosterone[5] and prostate-specific antigen (PSA) levels in metastatic CRPC.[6-8] Although the use of estrogens is well-tolerated, a high risk of cardiovascular events has been reported; therefore, the concomitant use

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of low-dose oral acetylsalicylic acid (ASA) has been investigated to reduce the risk of cardiovascular events, with major bleeding observed.[9,10] Because the availability of novel antiandrogens in clinical practice is very recent and because of the significant toxicity of docetaxel in the treatment of patients with CRPC, a clinical need exists for other therapeutic options for CRPC to avoid chemotherapy. Owing to the biologic and clinical efficacy of the use of estrogens in treating metastatic prostate cancer, we designed a phase II study of low-dose EE with concomitant low-dose ASA in patients with advanced CRPC.

## Patients and Methods

### *Eligibility Criteria*

The present study included patients with histologically confirmed advanced prostate adenocarcinoma that had relapsed after previous treatment with luteinizing hormone-releasing hormone analogues and antiandrogens. Patients started EE if the following criteria were met: positive bone scan findings and a $\geq$ 25% increase in the PSA level (PSA $>$ 2 ng/mL) for patients without measurable disease or new metastatic lesions revealed by a bone scan and a $\geq$ 25% increase in a bidimensionally measurable tumor mass with or without disease progression according to the PSA value.

All the patients had a baseline Eastern Cooperative Oncology Group performance status of $\leq$ 2, and adequate hematologic (leukocyte count $>$ 3000/mm$^3$; hemoglobin $>$ 10 g/dL, platelet count $>$ 100,000/mm$^3$), renal (serum creatinine $<$ 2.0 mg/dL), and hepatic (serum bilirubin $<$ 2.0 mg/dL) function.

Eligible patients had no history of arterial thromboembolic events, no active bleeding, and a low risk of bleeding. Patients with history of severe cardiovascular disease, infection, uncontrolled diabetes, or immobilization were excluded from receiving low-dose EE. EE and ASA were discontinued in any patient who developed pulmonary embolism, arterial thrombosis, or any cardiovascular or bleeding event or whose platelet count decreased to $<$ 50,000/mm$^3$. The ethics committee of Cremona Hospital approved the study, and all patients provided written informed consent. The use of bisphosphonates was allowed for all patients presenting with bone metastases.

### *Treatment Plan*

Patients received an EE dose of 150 μg daily (50 μg 3 times daily) with an ASA dose of 100 mg/daily (the standard dose used for prophylaxis for cardiovascular events).[11,12] Treatment was continued until disease progression was documented on the basis of the serum PSA level, testosterone concentration, radiographic imaging findings, and clinical findings. Safety and dosage compliance were evaluated on day 15 of cycle 1 and day 1 of each subsequent cycle, at treatment discontinuation, if applicable, and at the end of the study. Treatment with EE was discontinued if significant toxicity occurred or in the case of disease progression.

### *Response Assessments*

The serum PSA level was measured every 3 weeks. The PSA response rate was defined as the proportion of patients with a $\geq$ 50% decrease in the PSA concentration from the pretreatment baseline PSA value. PSA progression was defined as an increase from nadir of $\geq$ 25% and $\geq$ 2 ng/mL.[13] Progression-free survival (PFS) was defined as the interval from the start of EE therapy until PSA progression, radiographic progression, and/or symptomatic progression and was calculated using Kaplan-Meier estimates (Stata/IC, version 12). The pain reported by the patient was measured at baseline and then every 6 weeks using a translated form of the McGill Melzack pain questionnaire. The pain response was defined as at least a 2-point reduction of the pain intensity scale or the complete disappearance of pain.[14,15] The obtained results had to be confirmed by 2 consecutive evaluations performed $\geq$ 3 weeks apart, without any increase in analgesic consumption. The laboratory tests were performed at baseline and then every 4 weeks. The serum testosterone levels were measured only in those patients who experienced a PSA increase with stable disease.

The radiologic investigations included abdominal and pelvic computed tomography or magnetic resonance imaging, bone scan, and chest radiographs. All measurable diseases were re-evaluated at 8-week intervals. In all cases, a baseline electrocardiogram and echocardiogram were obtained, and further active cardiologic follow-up was performed, if indicated. Bone disease progression was defined as the appearance of any new bone lesion or the progression of existing bone metastases. A dental examination, including orthopantomography, was performed in all patients at baseline, with active dental surveillance performed every 3 months.

### *Treatment-Related Adverse Events*

Toxicity was defined using the National Cancer Institute Common Toxicity Criteria, version 3.0. Treatment was delayed at the first occurrence of any grade 2 toxicity and administered at the same dose after returning to grade 1 or better. In the case of grade 3 or 4 toxicity, treatment was interrupted, and a maximum of 3 weeks was allowed for recovery. In the case of a second episode of grade 3 or 4 toxicity in the same patient, treatment was resumed after recovery, but the subsequent dose of EE was reduced.

### *Statistical Analysis*

The primary endpoint was the PSA response. At the conception of the present study, no robust data were available regarding the use of EE in patients with CRPC. Assuming a response rate of approximately 10% with regard to other hormonal therapies for advanced CRPC and a target level of interest of 30%, with an $\alpha$ of 0.05 and a $\beta$ of 0.80, a sample size of 25 patients was planned in accordance with Simon's minimax design. An incremental accrual of 20% of patients was planned owing to the possible loss of patients during the follow-up period. The secondary endpoints were the median PFS and the pain response. PFS was determined using the Kaplan-Meier method to provide the median value and 95% confidence intervals, and the log-rank test was performed to compare the patients stratified by the PSA response.

## Results

From April 2014 to February 2015, 32 patients were enrolled to receive low-dose EE with low-dose ASA and were evaluable for efficacy analysis. Of the 32 patients, 4 were already receiving treatment with ASA because of other concomitant comorbidities. The characteristics of the 32 patients are listed in Table 1. The median age was 62 years (range, 58-76 years). The median basal PSA level was 11.5 ng/dL, and the median PSA level at nadir was 5.6 ng/dL. The median duration of androgen deprivation therapy

**Table 1** Patient Characteristics

| Characteristic | Value |
|---|---|
| Enrolled patients (n) | 32 |
| Age (years) | |
| Median | 62 |
| Range | 58-76 |
| Laboratory test results | |
| PSA (ng/mL) | |
| Median | 11.5 |
| Range | 2.5-259 |
| Hemoglobin (g/dL) | |
| Median | 11 |
| Range | 9.1-13.6 |
| ALP (U/L) | |
| Median | 161 |
| Range | 48-1115 |
| LDH (U/L) | |
| Median | 248 |
| Range | 82-1213 |
| ECOG performance status (n) | |
| 0 | 18 |
| 1 | 10 |
| 2 | 4 |
| Gleason grade (n) | |
| <8 | 19 |
| ≥8 | 13 |
| Duration of androgen deprivation therapy (years) | 7 |
| Metastatic sites (n) | |
| Bone | 31 |
| Lymph node | 20 |
| Visceral | 3 |
| Lines of therapy | |
| 1 | 23 |
| >1 | 9 |
| Pain present | 24 |
| Pain requiring opiates | 10 |

Abbreviations: ALP = alkaline phosphatase; ECOG = Eastern Cooperative Oncology Group; LDH = lactate dehydrogenase; PSA = prostatic-specific antigen.

before starting EE was 7 years. Of the 32 patients, 31 (96.8%) had bone metastases.

During EE-based treatment, a decrease in the PSA level of ≥ 50% was observed in 19 patients (59.3%; 95% CI, 41%-76%; Table 2). The response was confirmed at week 4 after the second PSA level evaluation. A decrease in the PSA level of ≥ 30% and ≥ 90% was reported in 23 (71.8%) and 6 (18.7%) patients, respectively. The waterfall plot for the PSA response is shown in Figure 1.

At the analysis (May 1, 2016), with a median treatment follow-up period of 10 months, the median PFS was 9.4 months (95% CI, 6.5-14.1 months). Of the 32 patients, 7 (21.8%) had not developed disease progression. The median PFS was 14.4 months (95% CI, 10.7 months to not reached) for patients who experienced a PSA decrease of ≥ 50% and 5.5 months (95% CI, 2.8-7.7

**Table 2** Summary of Outcomes

| Variable | n (%) |
|---|---|
| Enrolled patients | 32 |
| PSA decline | |
| ≥30% | 23 (71.8) |
| ≥50% | 19 (59.3) |
| ≥90% | 6 (18.7) |
| Efficacy | |
| Median PFS (mo; 95% CI) | 9.4 (6.5-14.1) |
| Patients without PSA progression at 12 mo | 13 (40.6) |
| Patients with PSA progression at 24 mo | 1 (3.2) |
| Palliative response (95% CI) | 10 (41.6) |
| Median duration of palliative response (mo; 95% CI) | 8 (5.5-9.4) |

Abbreviations: CI = confidence interval; PFS = progression-free survival; PSA = prostatic-specific antigen.

months) for patients without a PSA decrease of ≥ 50% ($P < .0001$; Figure 2). However, no statistically significant difference was observed in patients treated with > 1 line of therapy ($P = .60$). The proportion of patients without PSA progression at 12 months was 40.6% (13 patients); 1 patient had no disease progression 24 months after the start of the combined therapies The median PSA level in the group of patients who experienced disease progression was 13.1 ng/dL. The main determination of progression was the biochemical PSA increase. In the 24 patients who reported pain at baseline, pain reduction was documented in 10 (41.6%; 95% CI, 16%-50%), and the median duration of the palliative response was 8 months.

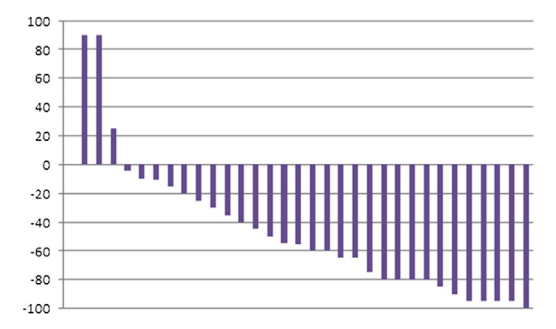
The regimen was generally well-tolerated, and no grade 3/4 toxicity was observed. No death related to adverse events was observed. One patient interrupted the combination of EE and ASA because of a cardiac event. No other thromboembolic, cardiovascular, or major bleeding complication events occurred during the use of EE and ASA. One patient reported grade 2 nausea and vomiting. Only 1 event of minor hematuria was reported, which completely and spontaneously resolved without the need for drug suspension. Two patients reported grade 1 asthenia. No other relevant toxicities were reported in our patients.

## Discussion

The results of our study suggest that low-dose EE with concomitant low-dose ASA as a thromboprophylactic agent is feasible and can achieve results in terms of the PSA response and PFS in patients with advanced CRPC. The EE and ASA combination was associated with a PSA response rate in 59.3% of our patients and a median PSF of 9.5 months.

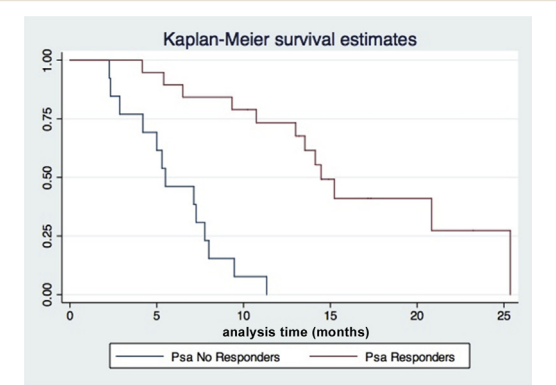
Recently, 2 novel antiandrogenic therapies, abiraterone and enzalutamide, were approved for the treatment of CRPC in the prechemotherapy setting. Abiraterone acetate is a potent and irreversible inhibitor of cytochrome P17 that blocks androgen synthesis, and enzalutamide is a nonsteroidal second-generation antiandrogen that blocks different steps in the androgen receptor signaling pathway. The efficacy of the combination of EE and ASA is modest compared with whose related to abiraterone and enzalutamide shown in larger and randomized trials.[4] In particular, in

**Figure 1** Waterfall Plot for Prostate-Specific Antigen Response




CRPC, abiraterone and enzalutamide resulted in a PSA response rate in 68% and 78% of patients, respectively, compared with 43% of patients receiving the combination of EE and ASA.[4] Moreover, the PFS for those receiving abiraterone and enzalutamide was longer than that for those receiving EE and ASA (16.5, 20, and 9.5 months for abiraterone, enzalutamide, and EE plus ASA, respectively). However, the availability in clinical practice of abiraterone and enzalutamide is recent. Previously, most patients with CRPC underwent chemotherapy only. However, considering the high incidences of adverse events related to chemotherapy, other agents were investigated for the treatment of CRPC. In the scenario of hormonal therapy, a biologic rationale exists for the use of estrogen therapy for CRPC. Estrogens inhibit the hypothalamic-pituitary-testicular axis through a negative feedback loop and, subsequently, testosterone production. Therefore, estrogen therapy exerts additional hormonal effects, decreasing continued stimulation of the androgen receptor necessary to fuel disease progression.[16] In addition, estrogens might decrease adrenal androgen production by inhibiting dehydroepiandrosterone and dehydroepiandrosterone sulfate synthesis.[16,17] Furthermore, secondary hyperexpression of estrogen receptors in prostate cancer has been observed after previous androgen deprivation therapy.[18,19] Several studies have also

**Figure 2** Progression-Free Survival Stratified by the Prostate-Specific Antigen Response (Psa)




shown a direct cytotoxic effect of estrogen on prostate cancer cells in vivo and in vitro.[20,21] Therefore, it is possible to speculate on a plausible clinical use for estrogens that might guarantee a new method of achieving castration in patients with prostate cancer resistant to LHRH agonist activity, with a direct cytotoxic effect.

In the clinical setting, several studies on the use of oral EE were performed that included men with advanced CRPC showing a PSA response of approximately 70% and a median PFS ranging from 10 to 15 months for those patients exhibiting a response.[6-8] Izumi et al[6] reported the positive outcomes of 24 Japanese patients with CRPC treated with orally EE at a dose of 1.5 mg/day, and Azuma et al[7] evaluated the safety profile and the efficacy of a combination therapy of etoposide and EE. Sciarra et al[8] reported the data from a large series of 112 patients with CRPC in whom $\geq$ 2 lines of androgen deprivation therapy had failed. A confirmed PSA response was found in 70.5% of the 112 patients. The median time to PSA progression was 15.10 months. In this context, the novelty of our study was the very low dose of EE (150 μg daily; 50 μg 3 times daily), suggesting the activity of EE on the PSA level of patients with CRPC is quite similar with lower dosages.

Other therapies for CRPC were investigated, such as diethylstilbestrol or fulvestrant.[22-25] However, although fulvestrant was well tolerated, it failed to produce a clinical or PSA response.[25] However, the combination of dexamethasone, aspirin, and the immediate addition of diethylstilbestrol resulted in neither a greater PSA response rate nor longer PFS compared with dexamethasone with deferred diethylstilbestrol.[23]

An increased risk of thromboembolic events during EE-based treatment has been reported.[8,26,27] In the study by Sciarra et al,[8] the toxicity (mainly thromboembolism) was the cause of treatment cessation for > 20% of patients. To avoid and prevent this possible complication, we enrolled only patients with a low risk of thromboembolic events, and concomitant low-dose ASA was administered with EE, because a recent meta-analysis reported an ASA dose of 100 mg is safe and adequate for primary cardiovascular disease prevention.[28] In our study, the concomitant assumption of ASA with EE might explain the possible absence of thromboembolic events in the treated cohort. Moreover, all other adverse events related to EE were reported in smaller percentages of patients, suggesting that low-dose EE is adequate in term of safety.[29]

Patients with advanced CRPC usually have bone metastases and a high risk of developing thrombocytopenia, which might increase the risk of bleeding associated with ASA used as thromboprophylaxis. Although almost all our patients had bone metastases, no major bleeding event was reported, suggesting that low-dose ASA is a safe prophylactic measure.

However, our study had several limitations. First, our study included a small number of patients, precluding possible definitive conclusions. Second, the absence of survival as an endpoint, using instead only the PSA response, and the absence of data on androgen levels and their changes during EE treatment were also shortcomings. Finally, PFS is a mixed endpoint that included PSA progression, clinical progression, and disease progression.

## Conclusion

Our results suggest that low-dose EE combined with low-dose ASA as thromboprophylaxis is a safe regimen with activity in

advanced CRPC. Because low-dose EE is both less expensive and more readily available, its clinical use should be investigated as an addition to novel hormonal therapies for prostate cancer to improve the cure rates and prolong the period to the start of first-line chemotherapy.

### *Clinical Practice Points*

- Low-dose EE with concomitant low-dose ASA as thromboprophylaxis is feasible and achieve results in terms of the PSA response rate and PFS in patients with advanced CRPC.
- The concomitant use of ASA with EE was possibly the reason for the absence of thromboembolic events in our study.
- The clinical use of low-dose EE should be investigated as an addition to novel hormonal therapies for prostate cancer.

## Disclosure

The authors declare that they have no competing interests.

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