Original Study

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

Giandomenico Roviello,[1,2] Laura Zanotti,[2] Angela Gobbi,[2] Martina Dester,[2] Daniele Generali,[2,3] Chiara Pacifico,[4] Maria Rosa Cappelletti,[2] Alberto Bonetta[5]

## 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.

*Clinical Genitourinary Cancer,* Vol. ■, No. ■, ■-■ 
**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 of low-dose oral acetylsalicylic acid (ASA) has been investigated to

[1]Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy
[2]Molecular Therapy and Pharmacogenomic Unit, ASST di Cremona, Cremona, Italy
[3]Department of Medical, Surgery and Health Sciences, University of Trieste, Trieste, Italy
[4]Department of Medical, Surgical and Neurological Sciences, University Hospital of Siena, Siena, Italy
[5]Department of Radiotherapy, ASST Cremona, Cremona, Italy

Submitted: Jul 7, 2016; Revised: Aug 24, 2016; Accepted: Aug 26, 2016

Address for correspondence: Giandomenico Roviello, MD, Department of Molecular and Translational Medicine, University of Brescia, Viale Europa, Brescia 11-25123, Italy
E-mail contact: giandomenicoroviello@gmail.com

1558-7673/$ - see frontmatter 
http://dx.doi.org/10.1016/j.clgc.2016.08.024

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