Low-Dose Estramustine Phosphate and Concomitant Low-Dose Acetylsalicylic Acid in Heavily Pretreated Patients With Advanced Castration-Resistant Prostate Cancer

Roberto Petrioli,[1] Giandomenico Roviello,[1] Anna I. Fiaschi,[2] Letizia Laera,[1] Vincenzo Bianco,[5] Roberto Ponchietti,[3] Gabriele Barbanti,[4] Edoardo Francini[5]

Abstract

Several new drugs with different mechanisms of action have been recently developed for the treatment of castration-resistant prostate cancer (CRPC). However, few data are available for the efficacy of other treatment options after disease progression occurs after therapy with new agents. Estramustine phosphate (EMP) previously demonstrated activity and manageable toxicity in advanced CRPC, with thromboembolic events sometimes reported with its use. The current phase 2 study suggested that low-dose EMP with concomitant low-dose acetylsalicylic acid as thromboprophylactic agents may achieve some activity in heavily pretreated advanced CRPC patients.

Background: The aim of this phase 2 study was to evaluate the activity and tolerability of low-dose estramustine phosphate (EMP) with concomitant low-dose acetylsalicylic acid (ASA) as a thromboprophylactic agent in heavily pretreated patients with advanced castration-resistant prostate cancer. **Methods:** Patients received 420 mg of oral EMP twice daily and oral ASA 100 mg once daily. The primary endpoint was prostate-specific antigen response. All of the patients had been previously treated with docetaxel and abiraterone acetate, and 12 had also received cabazitaxel. **Results:** Thirty-one patients were enrolled. Prostate-specific antigen response was observed in 9 patients (29.0%; 95% confidence interval [CI], 14-48). Median progression-free survival was 3.6 months (95% CI, 2.2-5.6), and median overall survival was 7.6 months (95% CI, 6.9-9.7). Treatment was generally well tolerated, and no grade 3/4 toxicity was observed. Ten patients (32.2%) had grade 2 nausea and vomiting. No cardiovascular event and no major bleeding occurred. No venous thromboembolism event was observed. **Conclusion:** Low-dose EMP with concomitant low-dose ASA seems to be a safe treatment option with some activity for patients with advanced castration-resistant prostate cancer who have been heavily pretreated.

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Introduction

Prostate cancer is the second leading cause of cancer-related death in men in most Western countries. Advanced and metastatic prostate adenocarcinoma (castration-resistant prostate cancer [CRPC]) has initially been traditionally managed by androgen-deprivation therapy, which involves either surgery (bilateral orchiectomy) or administration of gonadotropin-releasing hormone agonists or antagonists.[1] After androgen-deprivation therapy, 2 large randomized trials have provided substantial support in favor of the role of chemotherapy in the treatment of CRPC by demonstrating that docetaxel plus prednisone improves survival compared to older regimens and significantly ameliorates quality of life.[2,3] Therefore,

[1]Medical Oncology Unit
[2]Pharmacology Unit
[3]Urological and Andrological Unit
[4]Department of Urology
Santa Maria alle Scotte Hospital, University of Siena, Italy
[5]Medical Oncology Unit, Policlinico Umberto I Hospital, University of Rome, Rome, Italy

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Address for correspondence: Roberto Petrioli, MD, Medical Oncology Unit, University of Siena, Viale Bracci, 53100, Siena, Italy
Fax: +390577586231; e-mail contact: r.petrioli@ao-siena.toscana.it

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docetaxel has been considered the standard of care for first-line treatment of advanced CRPC.[2]

From 2010, several new agents with different mechanisms of action have been developed for the treatment of prostate cancer. These include cabazitaxel (CBZ),[4] sipuleucel-T,[5] and a new class of oral antiandrogen drugs such as abiraterone acetate (AA) or enzalutamide.[6,7] Finally, radium-223 has improved overall survival (OS) in men with symptomatic CRPC and bone metastases.[8]

Advanced CRPC patients who maintain a reasonable performance status after failure of docetaxel therapy might be considered for another line of treatment. Even if the optimal sequencing of these new agents has not yet been established, CBZ has been demonstrated to be effective in men previously treated with docetaxel as well as in subjects previously treated with the new hormonal drugs AA or enzalutamide.[9-11] However, in the TROPIC trial, 5% of patients died within 30 days of the last CBZ infusion, with severe neutropenia and its clinical consequences the most frequent cause of death.[4] Moreover, few data are available regarding the efficacy of other treatment options after progression of disease after docetaxel, AA, and CBZ therapy. Docetaxel rechallenge—that is, docetaxel reintroduction in patients who have been previously treated with this drug as first-line therapy—is another treatment option in advanced CRPC patients.[12]

The nitrogen mustard derivative of estradiol-17β-phosphate estramustine phosphate (EMP) previously demonstrated some activity in prostate cancer. Its antitumor properties are the result of its ability to interfere with microtubule dynamics and reduce plasma testosterone levels.[13] In the past, EMP has been investigated as a treatment option for prostate cancer in combination with other chemotherapy drugs such as docetaxel, and in 2007 a meta-analysis confirmed the benefits of EMP added to chemotherapy.[14] A meta-analysis of docetaxel-based therapy with EMP versus docetaxel-based chemotherapy in the treatment of CRPC patients reported no survival advantage for docetaxel combined with EMP.[15]

However, to our knowledge, there are no data about EMP used as a single-agent therapy in patients with CRPC who have been previously treated with the new drugs AA and CBZ.

Despite EMP being generally well tolerated, thromboembolic events (TE) associated with its use have been reported, especially when combined with other chemotherapeutic agents.[14] It is well known that cancer patients have an increased risk of TE compared to healthy subjects, and advanced age, comorbidities, and their subsequent therapies represent relevant risk factors for TE.[16] In this regard, the concomitant use of low-molecular-weight heparin or low-dose oral acetylsalicylic acid (ASA) as thromboprophylactic agents has been investigated in patients at high risk of TE, and their use has been associated with a reduction in the risk of TE with no concomitant major bleeding.[17,18]

On the basis of these previous experiences, we performed a phase 2 study to evaluate the activity and safety of low-dose EMP with concomitant low-dose ASA as a thromboprophylactic agent in patients with advanced CRPC who have been heavily pretreated.

Patients and Methods

Eligibility Criteria

This study involved patients with histologically confirmed, measurable, or evaluable advanced prostatic adenocarcinoma whose disease had progressed after therapy with docetaxel and AA. Patients who had undergone previous treatment with CBZ were also admitted. Patients initiated therapy with EMP provided that they met at least one of the following criteria: a positive bone scan and a $\geq$ 25% increase in prostate-specific antigen (PSA; PSA $>$ 2 ng/mL) compared to baseline on 2 successive measurements separated by at least 2 weeks for patients without measurable disease; and new metastatic lesions revealed by a bone scan and a $\geq$ 25% increase in a bidimensionally measurable tumor mass with or without disease progression on the basis of the PSA value.

All patients had a baseline Eastern Cooperative Oncology Group performance status of $<$ 2, as well as adequate hematologic (leukocytes $>$ 3000/mm^3; hemoglobin $>$ 10 g/dL, platelets $>$ 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 deep-vein thrombosis or arterial TE, had no active bleeding, and were not considered to be at high risk of bleeding. Patients with relevant risk factors for TE, such as a history of severe cardiovascular disease, infections, uncontrolled diabetes, and immobilization, were excluded from the study. EMP and ASA were discontinued in any patient who developed deep-vein thrombosis, pulmonary embolism, arterial thrombosis, or any cardiovascular or bleeding event, or whose platelet count decreased to $<$ 50,000/mm^3.

The study was approved by the ethics committee of Siena University, and all patients provided written informed consent.

Bisphosphonates were allowed in all patients presenting bone metastases.

Treatment Plan

Patients received oral EMP at a daily dose of 420 mg and oral ASA 100 mg/day. A slightly reduced dose (420 mg) compared to the standard dose of EMP (560 mg) was chosen for this study to further limit the risk of toxicity, because all the patients had been heavily pretreated. Acetylsalicylic acid (ASA) 100 mg was chosen because this dose was largely provided as prophylaxis for thrombosis in trials of patients at high risk of occlusive vascular events.[19,20] Treatment was continued until disease progression was documented on the basis of serum PSA and testosterone concentration, radiographic imaging, and clinical findings. Safety and dosage compliance were evaluated on day 15 of cycle 1 and on day 1 of each subsequent cycle, at the time of treatment discontinuation (if applicable), and at the end-of-study visit. Treatment with EMP was discontinued if significant toxicity occurred or if the attending physician concluded that it was not effective.

Response Assessments

Tumor response in patients with measurable lesions was evaluated using the Response Evaluation Criteria in Solid Tumors.[21] Serum PSA was measured every 3 weeks: a PSA response rate was defined as the proportion of patients with $\geq$ 50% decrease in PSA concentration from the pretreatment baseline PSA value, which was confirmed after $\geq$ 4 weeks by an additional PSA evaluation; PSA progression was defined as an increase from the nadir of at least 25% and $\geq$ 2 ng/mL.[22] Median OS was measured from the start of EMP treatment until death or censoring. Progression-free