Effective and Safe Administration of Low-Dose Estramustine Phosphate for Castration-Resistant Prostate Cancer

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Abstract

Despite the favorable toxicity profile at the standard dose of 560 mg daily, the tolerability and toxicology of estramustine phosphate (EMP) have been a cause for concern at administration. Moreover, we do not know whether a lower dose of 280 mg of EMP daily can be administered with some efficacy and fewer side effects. The results of our phase II study suggest that low-dose EMP is a safe treatment option with the same efficacy in patients with castration-resistant prostate cancer.

Background: We evaluated the efficacy and safety of low-dose estramustine phosphate (EMP) in Japanese patients with castration-resistant prostate cancer (CRPC). **Patients and Methods:** The present study was a single-arm, nonrandomized prospective study in which all patients received EMP orally twice daily for a total dose of 280 mg/day. A total of 31 patients with CRPC were enrolled from December 2009 to December 2012 at 5 institutions in Japan. The primary endpoint was the prostate-specific antigen (PSA) response, defined as a 50% decline in the serum PSA level, confirmed $\geq$ 3 weeks later. The secondary endpoints included the objective response rate, interval to PSA progression, PSA response duration, progression-free survival, disease-specific survival, overall survival, safety, and quality-of-life assessment using the Functional Assessment of Cancer Therapy-Prostate scores. **Results:** Ten patients (32%) had a PSA response, and no patient had an objective response. The treatment was well tolerated, and the most frequent toxicities were grade 1 to 2 nausea/vomiting, anorexia, and gynecomastia. The median interval to PSA progression was 140 days (95% confidence interval [CI], 117-260 days). The PSA response duration was 119 days (95% CI, 49-219 days). The median progression-free survival was 213 days (95% CI, 167-422 days). The 3-year disease-specific survival and overall survival rates were 68.6% (median not reached; 95% CI, 33 months to not available) and 59.9% (median 42 months, 95% CI, 28 months to not available), respectively. **Conclusion:** Low-dose EMP seems to be a safe treatment option with some efficacy in patients with CRPC.

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Introduction

The vast majority of patients with advanced prostate cancer respond to initial androgen-deprivation therapy (ADT). However, most of them develop progression to a lethal state known as castration-resistant prostate cancer (CRPC), with serial increases in prostate-specific antigen (PSA) levels or radiologic or clinical progression despite castrate androgen levels. In 2004, 2 large randomized trials proved substantial progress in the treatment of CRPC

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by demonstrating that docetaxel improves survival compared with conventional older regimens.[1,2] However, most patients who received docetaxel experienced severe adverse events, such as neutropenia, especially in Japanese populations.[3,4] Thus, when this low-dose estramustine phosphate (EMP) trial was started, a safe, noncytotoxic, and effective treatment for patients with CRPC was still needed.

EMP, the nitrogen mustard derivative of estradiol-17β phosphate, has antitumor properties against prostate cancer because its antimitotic properties interfere with microtubule dynamics and reduce serum testosterone levels.[5] EMP was introduced in the early 1970s and has been predominantly evaluated as a second-line option for patients with CRPC, particularly in combination with other chemotherapy drugs after the advent of PSA as a tumor marker.[6] In 2004, the randomized phase III Southwestern Oncology Group trial showed that a combination of docetaxel and EMP is superior to a regimen of mitoxantrone and prednisone.[2] Additionally, a meta-analysis of 5 randomized clinical trials of patients who received chemotherapy with or without EMP to assess whether the addition of EMP improved survival showed that EMP plus chemotherapy significantly improved the PSA response, increased the interval to PSA progression, and increased overall survival.[7]

Despite the favorable toxicity profile at the standard dose of 560 mg daily, the tolerability and toxicology of EMP have been a cause for concern at administration. Major adverse events include nausea and vomiting, which occur in about 40% of patients. However, in most cases, their severity will be moderate and the symptoms can be managed adequately.[5] Thromboembolic events are the more severe adverse events associated with the use of EMP. They can result in increased morbidity and mortality because of the increased risk of thromboembolic complications such as cardiovascular events, pulmonary embolism (PE), and stroke.[5]

The optimum dose of EMP for patients with CRPC remains unknown. Furthermore, we do not know whether low-dose EMP can be administered with the same efficacy as higher dose EMP but with fewer side effects. Therefore, we conducted a phase II study to evaluate the efficacy and safety of low-dose EMP in Japanese patients with CRPC.

Patients and Methods

Patients

The present study was a prospective single-arm phase II multicenter trial of men aged 20 to 85 years, with prostate cancer progression during hormonal therapy. All the patients had a baseline PSA level of $>$ 2 ng/mL and cancer that was refractory to a luteinizing hormone-releasing hormone (LHRH) agonist or bilateral orchiectomy or antiandrogen therapy. Patients who had withdrawn from antiandrogen therapy were required to have 1 PSA level that was greater than the last prewithdrawal PSA level if treated with an antiandrogen for $\leq$ 3 months. Patients who had withdrawn from $>$ 3 months of antiandrogen therapy were required to have 2 consecutive increases in the PSA level after a postwithdrawal nadir $\geq$ 6 weeks after treatment withdrawal. The eligibility criteria also included an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2; acceptable bone marrow, liver, and kidney function; no previous treatment with estrogenic compounds such as EMP or diethylstilbestrol; no active thrombophlebitis or hypercoagulability; and no history of pulmonary embolus or cerebral infarction. Also, $\geq$ 4 weeks had to have elapsed between any previous surgery and/or radiation therapy and entry into the present study.

The pretreatment evaluation included the clinical history, physical examination (with weight, height, and PS recorded), computed tomography (CT) scan of the abdomen and pelvis, chest radiography, and bone scintigraphy. Blood tests, including measurement of hematologic and chemical values, and serum PSA measurement were also performed. Quality of life (QOL) was assessed using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire as a baseline.

Study Design

The present study was undertaken at 5 institutions: Kyoto University Hospital (Kyoto, Japan), Miyazaki University Hospital (Miyazaki, Japan), Japanese Red Cross Otsu Hospital (Otsu, Japan), Kyoto City Hospital (Kyoto, Japan), and Kobe City Medical Center General Hospital (Kobe, Japan). Each patient provided written informed consent before registration. The present study was conducted according to the Declaration of Helsinki and was approved by the appropriate ethics committee of every institution. The patients were enrolled from December 2009 to December 2012. EMP was administered orally twice daily for a total dose of 280 mg/day, and LHRH agonist therapy was continued if it had been previously administered. The study was conducted for 24 weeks, and patients were allowed to continue EMP treatment beyond the 25-week assessment at the discretion of the investigator until clinical progression, disease progression, or the occurrence of unacceptable safety or tolerability issues were observed. Surgery or radiation therapy for local and/or metastatic lesions, chemotherapy, and immunotherapy were not permitted during the study period. Corticosteroid and bisphosphonate administration was also not allowed. EMP was not administered with milk products or calcium to ensure optimal absorption.

The patients were discontinued from the study if they had objective disease progression, clinical progression, or the development of adverse events or toxic effects. However, they continued to receive EMP for $\geq$ 12 weeks in the presence of PSA progression. The grade of toxicity was determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. Treatment could be interrupted if grade 2 or greater toxic effects occurred and started again once the toxic effects had improved to grade 1 or less. Patients could start taking the study drug again at a reduced level if possible.

The complete blood count, chemistry panel, and PSA levels were evaluated monthly until week 24, and the PSA levels were assessed every month thereafter during EMP administration. Imaging studies were repeated at weeks 12 and 24 and every 3 months thereafter during EMP administration. Adverse events and the ECOG-PS were recorded at each clinic visit. The adverse events were determined according to the CTCAE, version 3.0. The FACT-P questionnaire was administered at baseline and weeks 12 and 24 during therapy.

Outcomes

The primary endpoint was the PSA response, defined as a 50% decline in the serum PSA level, with confirmation $\geq$ 3 weeks later.