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Original article

Combination chemotherapy with docetaxel, estramustine and suramin for hormone refractory prostate cancer

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Abstract

Purpose: To investigate more effective chemotherapy against hormone refractory prostate cancer (HRPC) with the combination of estramustine (EM), docetaxel, and suramin.

Patients and Methods: A total of 42 patients with symptomatic, progressive HRPC were included in this study. We evaluated the activity of the following schedule: EM 10 mg/kg orally daily on Days 1 to 21 every 28 days, docetaxel 70 mg/m^2 IV on Day 2 every 28 days and a total doses of 2150 mg of suramin in every cycle. Treatment was continued until disease progression or excessive toxicity.

Results: Median follow-up was 23.4 months. A median of 8.8 consecutive cycles was administered per patient. In the 25 patients with lymphadenopathy, there were three (12%) complete and 18 (72%) partial responses for a measurable disease response rate of 84%. Levels of prostatic specific antigen (PSA) decreased by greater than 50% in 100% of patients and by greater than 90% in 76.2%. The median time to progression was 57 weeks and median overall survival was 132 weeks. A decline in PSA of $\geq$50% lasting $\geq$30 days was significantly associated with a prolonged median time to progression and median overall survival. Tumor volume reduction and/or antitumor treatment effects were observed in 88% of patients. A significant decrease in mean pain score from 7.8 (range, 6–10) to 2.2 (range, 0–4) ($P < 0.001$) was achieved in 78%. Of patients with bone metastasis, 30.5% demonstrated a partial response. The mean Eastern Cooperative Oncology Group (ECOG) performance score improved from 2.8 to 1.5 at the end of treatment period. There was no therapy-related death. The predominant toxicities were Grade 3 or 4 leukopenia in 33.3%, anemia in 21%, thrombocytopenia in 21.4%, cardiac ischemia in 4.7%, and rash in 4.7%.

Conclusion: The combination of docetaxel, EM, and suramin is a highly effective regimen for HRPC. Although hematologic and gastrointestinal toxicities were modest, these were easily managed medically.

Keywords: Estramustine; Docetaxel; Suramin; Drug therapy; Prostatic neoplasms

1. Introduction

Hormone refractory prostate cancer (HRPC) clinically defines as metastatic or locally advanced prostate carcinoma that become hormone independent and progress after first and secondary endocrine treatment. It still remains an incurable disease, with a median survival time less than 1 yr [1]. Management of this hormone refractory stage of prostate cancer remains a significant challenge to the clinician. The development of new classes of drugs and examination of different combinations of drugs all support the contention that important studies are being made toward improving quality of life and survival of the patient with HRPC.

Estramustine phosphate is rapidly dephosphorylated in vivo to estramustine, which dysregualtes normal microtubule assembly, resulting in cell growth inhibition in human prostate cancer cells line [2,3]. Taxanes (paclitaxel and docetaxel) bind to different sites on B tubulin (Tau vs. N-terminal) affect different mitotic structures (centrosome vs. mitotic spindle), and arrest cells at different phases of the cell cycle (S vs. G2M) [4]. The mechanisms of antitumor activity of the taxanes are the inhibition of depolymerization of microtubules and inhibition of the antiapoptic effect of bcl-2 [5]. Eighteen Phase II trials of single agent EM in 634 patients showed objective measurable responses in only 19% [6]. However, the synergy noted when estramustine (EM) is combined with other drugs that target microtubule action such as taxanes. EM plus paclitaxel had encouraging results in HRPC [7,8]. Docetaxel, a semisyn-

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thetic taxoid, disrupts the cellular microtubular network, promoting assembly of stable microtubules and inhibiting disassembly approximately twice as effectively as paclitaxel [9]. Further, in vitro, docetaxel is approximately 100-fold more effective in phosphorylating bcl-2 than paclitaxel [5]. In addition, tissue culture studies suggest that the dose required for 50% inhibition of growth by docetaxel in combination with EM is 60-fold lower than for paclitaxel plus EM [10]. Finally, docetaxel causes less neurotoxicity than paclitaxel. Suramin, a polysulphonated naphthyl urea, originally used as an antihelminth preparation. Suramin inhibits the action of hormone-depended and -independed growth factors, among which are transforming growth factors alpha and beta, insulin growth factor, and fibroblast growth factor [11]. Several reports have suggested that suramin possesses clinically significant antitumor activity as reflected by measurable disease responses, swift and durable decline in prostate-specific antigen (PSA) levels, pain relief, and a relatively long time to disease progression [12,13]. A recent randomized study of 460 symptomatic hormone refractory cancer patients comparing suramin plus hydrocortisone to placebo plus hydrocortisone revealed significant pain relief (43% vs. 28%), median duration of pain response (240 vs. 69 days), and 50% PSA declines (33% vs. 16%) [14]. Even though various novel combination regimens with partly encouraging results regarding subjective response have been reported in clinical trials, but overall survival has not been affected by any regimen to date.

Based on encouraging clinical data and the suggestion of efficacy with tolerable toxicity in Phase I and II studies, we conducted a prospective study of docetaxel, EM, and suramin for Iranian patients with HRPC.

2. Materials and methods

2.1. Patient selection

Eligible patients demonstrated histologically documented metastatic adenocarcinoma of the prostate with progressive systemic disease despite androgen deprivation, and no prior chemotherapy. All patients were required to have ceased all medical hormonal therapy as well as to have completed any radiation therapy at least 4 weeks before the initiation of the protocol. All patients had undergone bilateral orchiectomy. Pretreatment evaluation included medical history, physical examination, complete blood count with differential and platelet counts, chemistry profile, serum PSA level, 24-h creatinine clearance, 12-lead electrocardiogram, chest X-ray, bone scan, computerized tomography (CT) and magnetic resonance imaging. Other inclusion criteria were also to have Eastern Cooperative Oncology Group (ECOG) performance score 0–3, baseline granulocytes count more than 1500/ μL, platelet count more than 100,000/ μL, hemoglobin 10 g/dL or greater, adequate renal function defined as serum creatinine 1.5 times or less than upper limit of normal (ULN), adequate liver function defined as bilirubin less than ULN and aspartate transaminase less than 1.5 times the ULN, adequate cardiac function and a life expectancy of more than 6 months. Patients with a history of other malignancy within the last 5 yr, uncontrolled or severe cardiovascular disease, paranchymal brain metastases, thromboembolism, clinically significant neuropathy, prior immunotherapy, prior chemotherapy or concurrent use of exogenous corticosteroids were excluded from the trial. Each patient gave written informed consent.

2.2. Treatment regimen

The treatment consisted of 10 mg/kg EM orally divided into three daily doses on Days 1 to 21 every 28 days, 1 h before or 2 h after ingesting food. For 1-h every 21 days (on Day 2) 70 mg/m^2 docetaxel were administered IV. All patients received 8-mg dexamethasone IV 30 min before each docetaxel infusion. A loading dose of 1000 mg/m^2 suramin in 500 mL of 5% dextrose infused over 2 h on Day 1. One-hour infusions of 400, 300, 250, and 200 mg/m^2 were given on Days 2, 3, 4, and 5, respectively. Treatment schedule was repeated every 4 weeks for a minimum of four cycles. Patients who demonstrated response to therapy continued treatment until disease progression, complete response, the development of treatment—limiting toxicity, or withdrawal of consent. Patients did not receive concomitant anticoagulants routinely. Colony-stimulating factors were administered according to American Society of Clinical Oncology guidelines as needed. Furthermore, blood transfusion of platelets and red blood cells was performed for severe symptoms related to thrombocytopenia and anemia. Toxicity was graded according to National Cancer Institute common toxicity criteria (Version 2.0). If Grade 3 or 4 toxicity occurred, all subsequent cycles of therapy were interrupted until the toxicity resolved to less than Grade 2 and hematological parameters had recovered to at least met entry criteria. Patients who experienced any persistent ($\geq$4 weeks) or recurrent Grade 3 or 4 toxicity without significant antitumor response were removed permanently from study treatment. If patients' toxicity was higher than Grade 3, subsequent doses of docetaxel and suramin were reduced by 25% for the next cycle. The dose of EM was reduced by 25% in the case of severe gastrointestinal toxicity.

2.3. Evaluation

Systematic sextant biopsy of the prostate was performed. Measurable soft tissue disease was defined as any lesion 1 cm $\times$ 1 cm or greater in bidimensional measurements. Patients were evaluated for response by imaging studies every 8 weeks and systematic sextant biopsies were performed at the end of four cycles of chemotherapy. PSA levels were measured every 4 weeks. Pain status was evaluated using the Brief Pain Inventory [15]. Each night, patients scored their worst pain over the prior 24 h (daily worst