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Feasibility of 21-day Continuous Infusion of Epirubicin in Hormone-refractory Prostate Cancer Patients

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Abstract. *Background: Epirubicin (EPX) has been found to be active in hormone-refractory prostate cancer (HRPC) patients. Prolonged EPX infusion has never been investigated in this patient subset. Patients and Methods: A feasibility study was conducted in which EPX was administered in 21-day continuous infusion to 15 patients with HRPC. The EPX dose was 5 mg/m^2/daily for 21 consecutive days (one course). One week was allowed before starting the next course. Results: The patients received 1 to 6 courses (median 3). As a whole, the treatment was well tolerated. Nine patients did not develop any toxicity, while WHO grade 3 and 4 toxicities were recorded in 4 patients. Alopecia (WHO grade 1-2) was presented in 4 cases. Five patients attained >50% decrease in serum prostate-specific antigen (PSA). Conclusion: Prolonged EPX infusion is feasible and potentially active in the treatment of HRPC patients. Our data suggest caution in administering this treatment in patients bearing rheumatologic disease.*

Prostate cancer is the most commonly diagnosed malignancy among males in Italy and the second leading cause of cancer-related mortality (1).

Hormone-refractory prostate cancer still remains an incurable disease, with a median survival prospect of less than 12 months (2). There is no accepted standard systemic treatment for the disease at this stage. Cytotoxic agents have not demonstrated a significant impact on the outcome of treated cases (3). Epirubicin (EPX) has been repeatedly found to be an active cytotoxic agent in prostate cancer patients with hormone-refractory disease, either administered alone or in combination. When this drug was administered in a weekly schedule, tolerability was found to increase consistently (4-17). Prolonged EPX infusion has never been investigated in this patient subset. The rationale for giving EPX at a continuous infusion schedule is based on: i) the concept that a greater number of actively dividing cells are expected to be exposed to EPX when it is given over an extended period of time; ii) due to elimination of the high peak plasma levels, most toxic effects of EPX could be reduced; iii) the observations made by a pharmacokinetic study showing a greater intracellular EPX uptake with continuous infusion as opposed to bolus administration (18). We report here the results of a feasibility study of protracted EPX infusion in a group of advanced prostate cancer patients with hormone-refractory disease.

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Patients and Methods

Patients were considered eligible if they had histologically-confirmed prostate adenocarcinoma with metastatic bone disease and progressive disease to luteinizing-hormone releasing-hormone analogue (LHRH-A) administration in the presence of castrate levels of testosterone. Disease progression was defined by rising prostaste-specific antigen (PSA) levels (determined by two consecutive measurements at least 2 weeks apart), in addition to the appearance of a new lesion on bone scan and/or an increase in the size of a measurable lesion on a computed tomographic (CT) scan of the abdomen/pelvis or chest. All patients previously treated with anti-androgen in addition to LHRH-A (total androgen ablation) were required to undergo anti-androgen withdrawal. Patients were required to be off anti-androgens for at least 4 weeks, with further evidence of disease progression after stopping the anti-androgen therapy. Further inclusion criteria included age ≤75 years old, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-3, appropriate renal (creatinine ≤2 mg/dl), hepatic (bilirubin ≤2 mg/dl, AST and ALT ≤2.5 times upper limit of normal range), and hematological (WBC count

≥3.0x10^3/mL, neutrophils ≥2.0x10^3/mL, platelets ≥100x10^3/mL) functions at baseline, adequate cardiac function (ventricular ejection fraction >55%). One previous chemotherapy line without anthracyclines was permitted. Patients were excluded from the study for increase in PSA levels alone, severe uncontrolled co-morbidities, second malignancies, cardiac diseases and brain metastases. This study was approved by the Ethics Committee of the respective Institutions and was conducted in compliance with international guidelines regulating patient safety. All patients were required to give written informed consent before registration.

Treatment regimen. Treatment consisted of continuous intravenous infusion of EPX (Pharmacia, Milan, Italy) at a daily dose of 5 mg/m^2 for 21 consecutive days. EPX was diluted in normal saline for injection and infused continuously *via* a 7-day elastomeric pump (Baxter, Round Lake, IL, USA). All patients had a central venous access. The drug was administered on an outpatient basis. Cycles consisted of 3 weeks of treatment and 1 week of rest for a total EPX administration of 105 mg/m^2 every month. The dose and schedule was chosen on the basis of published results of a phase I study (18). Six chemotherapy cycles were planned, unless disease progression or unacceptable toxicity occurred. Previous androgen deprivation therapy was continued during the cytotoxic treatment, but no other antineoplastic treatments (including steroids) were allowed.

The EPX dose was planned to be reduced by 25% for an absolute neutrophil count <1.5x10^9/L and/or a platelet count <100x10^9/L. When the granulocyte count fell below 1.0x10^9/L or platelet count fell below 50x10^9/L, the drug was interrupted until acceptable blood levels returned. Patients requiring more than a 4-week delay of treatment were withdrawn from the study. If grade 3 or 4 hematological/non-hematological toxicities (excluding neurotoxicity) were observed during any cycle, then the patient dose was excalated to 75% for subsequent treatment weeks. Drug administration was discontinued in the event of grade 4 non-hematological toxicities and neurotoxicity of grade 3 or worse.

Assessment of response and toxicity. Pre-treatment evaluations included a complete medical history, physical examination, ECG, echocardiography, chest X-ray, bone scan, CT scan of the abdomen and pelvis (CT scan of the chest was performed only if clinically indicated), and laboratory studies, including a complete blood scan with differential, comprehensive chemistry profile, testosterone levels, prothrombin time, partial thromboplastin time and PSA. Clinical monitoring and a complete blood cell count assessment were performed weekly; serum electrolytes, ECG, and liver function tests were performed every 3 weeks. Chest X-ray, CT scans of the abdomen/pelvis and serum PSA were obtained after every 3 cycles during treatment and then every 3 months until the patient experienced disease progression. A bone scan was performed every 6 months. Echocardiography was performed every 6 months. All patients had to receive at least 2 months of treatment to be eligible for assessment of tumor response. In patients with tumor response or stable disease, the treatment was to be continued for 6 cycles; thereafter, further cycles of therapy were based on the clinician's choices. After completing the treatment plan, patients were monitored every 3 months. All patients were evaluated for PSA response, objective measurable disease response, if applicable, subjective response, time to disease progression and survival. A PSA decline ≥50%, confirmed by a second value at least 4 weeks later, was considered a PSA response. Tumor response was classified according to standard WHO criteria for measurable disease (19), if present, and documented by 2 assessments at least 4 weeks apart. A complete response (CR) was defined as a complete disappearance of all clinical, radiological, and biochemical evidence of disease for a minimum of 1 month. A partial response (PR) required a 50% or greater reduction in the sum of the products of the longest diameter and its perpendicular. Stable disease (SD) was indicated by a decrease of <50% or an increase of <25% in the product of the longest perpendicular diameters of measurable lesions lasting 3 months. Progressive disease (PD) was defined as the appearance of new lesions or an increase of ≥25% in the sum of the products of the longest diameter and its perpendicular compared with the lowest value recorded. Bone scans were considered stable if there were no new lesions in the 2 scans performed at baseline and after 6 months. All deaths and treatment discontinuations for toxicity or patient refusal were considered treatment failures. Bone pain was evaluated by means of a validated questionnaire according to Coleman (20). The items included the assessment of the performance status, analgesic consumption, and mobility, which produced a pain score from 0 to 16. Toxicity was evaluated according to World Health Organization (WHO) criteria (19).

Table I. *Patient characteristics.*

No.	15
Age years median (range)	66 (54-78)
ECOG performance status median (range)	1 (1-3)
Disease sites	
Bone	15/15 (100%)
Lymph nodes	6/15 (40.0%)
Previous treatments for hormone-sensitive prostate cancer	
LHRH-A±Anti-androgens	15/15 (100%)
Previous treatments for hormone-refractory prostate cancer	
Estramustine±Etoposide	4/15 (26.7%)
Mitoxantrone+Prednisone	1/15 (6.7%)
Steroids	5/15 (33.3%)
Patients evaluable for PSA variations	15/15 (100%)
Patients evaluable for measurable disease	1/15 (6.7%)
Patients evaluable for subjective response (bone pain)	15/15 (100%)

Results

Fifteen metastatic prostate cancer patients with disease refractory to androgen deprivation were treated. The patient characteristics were as follows (Table I): median age 66 years (range 54-78), median ECOG performance status 1 (1-3), all patients had painful bone metastases, 2 patients also had abdominal lymph node involvement. Previous treatments for

Table II. *Toxicity.*

GRADE	0	1	2	3	4
Neutrophils	11/15 (73.3%)	0	1/15 (6.7%)	3/15 (20.0%)	0
Plattelets	15/15 (100%)	0	0	0	0
Hemoglobin	15/15 (100%)	0	0	0	0
Nails	14/15 (93.3%)	0	1/15 (6.7%)	0	0
Nausea	9/15 (60.0%)	5/15 (33.3%)	1/15 (6.7%)	0	0
Asthenia	12/15 (80.0%)	2/15 (13.3%)	1/15 (6.7%)	0	0
Hepatic toxicity	14/15 (93.3%)	0	0	1/15 (6.7%)	0
Mucositis	13/15 (86.6%)	1/15 (6.7%)	0	1/15 (6.7%)	0
Alopecia	11/15 (73.4%)	2/15 (13.3%)	2/15 (13.3%)	0	0

For each patient the most severe instance of toxiccity was recorded

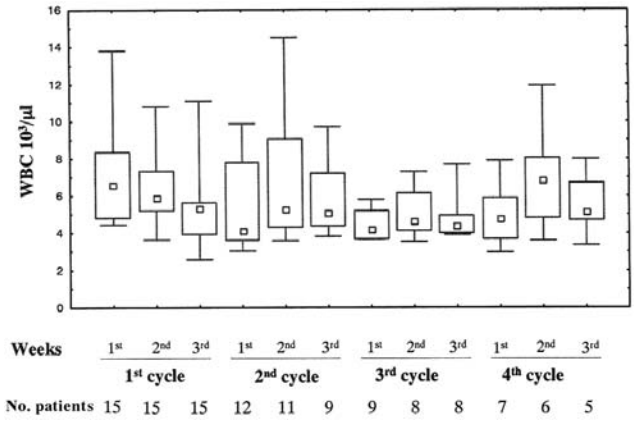

Figure 1. *Weekly profile of white blood cell variation during treatment (data are mean + SE + SD).*

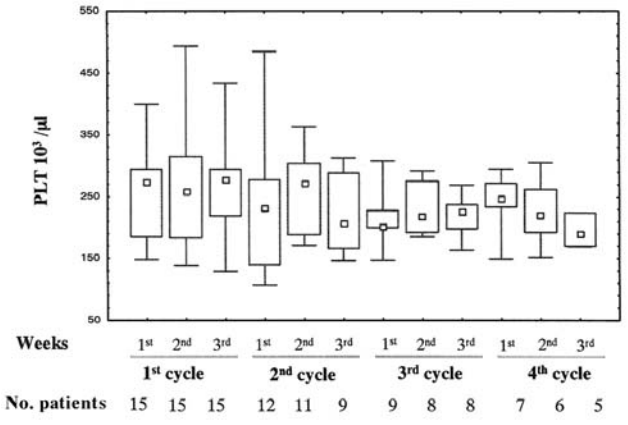

Figure 2. *Weekly profile of platelet variation during treatment (data are mean + SE + SD).*

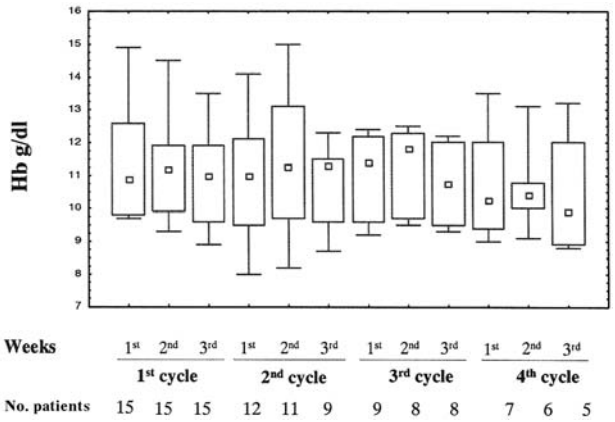

Figure 3. *Weekly profile of hemoglobin variation during treatment (data are mean + SE + SD).*

hormone-refractory disease consisted of estramustine ± etoposide in 4 patients, mitoxantrone + prednisone in 1, and steroids in 5. A median of 3 cycles were administered to each patient (range 1-6). As a whole, the treatment was well tolerated (Table II). Nine patients did not develop any toxicity. White blood cell, platelet and hemoglobin profiles did not reveal consistent variation of mean values (Figures 1, 2, 3). No patients developed platelet toxicity. Hemoglobin levels between 9.5 and 11 g/dl (corresponding to WHO grade 1-2) were found in about a half of the cases, but in most of them these values were already present at baseline conditions and did not change during treatment. Grade 3 or 4 toxicities were recorded in 4 patients. One patient developed grade 3 leukopenia and grade 3 mucositis: this patient has been concomitantly submitted to cervical radiation therapy (30 Gy) due to spinal cord compression. Another patient, with a

concomitant history of chronic alcoholic hepatitis and HBV infection, presented grade 3 hepatic toxicity and grade 3 leukopenia. Surprisingly, only 4 patients developed mild alopecia (grade 1 and 2). Two patients died while in treatment: 1 of them due to brain hemorrhage, and the other to respiratory insufficiency due to pulmonary fibrosis. This latter patient had a concomitant history of rheumatoid arthritis. Four patients ended the treatment plan. Treatment was interrupted in 11 patients due to progressive disease (5 patients, after 1, 2, 4, 4 and 5 cycles, respectively), thrombosis of the central venous access (2 patients, after 1 and 3 cycles), death (2 patients, after 1 and 2 cycles), and gastro-intestinal toxicity (2 patients, after 1 and 2 cycles), respectively. A treatment delay of 2 weeks was performed once due to leukopenia.

Five patients attained >50% decrease in serum PSA, lasting 1, 2, 3, 8 and 10 months, respectively. A PSA stabilization was obtained in 4 patients, and a PSA increase in 6 patients. Bone pain improved in 5 patients, did not change in 8, while it worsened in 2. In 1 patient the PSA decrease was accompanied by a dramatic decrease (>80%) of a pelvic mass (8 cm wide).

Discussion

Through recent developments in reliable portable pumps and safely implanted venous access systems, continuous infusion of chemotherapeutic agents has become feasible on an out patient basis. In a phase I and pharmacokinetic study, EPX administration, as a continuous infusion, was found to lead to greater intracellular drug levels as opposed to bolus injection. The recommended dose level was 6 mg/m^2 every day, but a daily dose of 5 mg/m^2, leading to a monthly cumulative dose of 105 mg/m^2, was found to be without toxicity. This latter dose was chosen to be administered in this pilot study involving elderly patients. As far as hematological toxicity is concerned, this feasibility trial showed that prolonged continuous infusion of EPX is very well tolerated in hormone-refractory prostate cancer patients. White blood cell decrease was negligible in all patients, with only 3 exceptions. One of these patients had been concomitantly exposed to radiation therapy, which presumably may have caused additional bone marrow toxicity. Concomitant radiation therapy in this patient could also have contributed to the onset of grade 3 mucositis, leading to an early treatment interruption. Grade 3 leukopenia occurred in another patient with a concomitant history of hepatic disease, who also developed grade 3 hepatic toxicity. Interestingly, alopecia was rarely observed and was mild. These data suggest that the common side-effects of EPX administration, such as bone marrow depression and alopecia, could be limited, and in some cases prevented, by eliminating the peak plasma levels. Concomitant radiation therapy and hepatic disease, however, could favor the onset of hematological and extra-hematological adverse events with this treatment modality. No acute cardiac toxicity was encountered. Due to the short follow-up, no data could be provided on late heart events.

The good tolerability notwithstanding, 6 patients interrupted the treatment plan early for causes other than disease progression. One patient died of a fulminant pulmonary syndrome after 1 chemotherapy cycle. Given the temporal relationship among treatment, onset of symptoms and death, a causal relationship must be considered. Pulmonary toxicity is a known side-effect of many cytotoxic drugs, such as cyclophosphamide, gemcitabine, bleomycin and taxanes (21). Anthracyclines have been reportedly found to increase the pulmonary toxicity of radiation therapy (22) but, to our knowledge, pulmonary fibrosis has never been described after administration of anthracyclines alone. The prolonged continuous infusion could have changed the drug toxicity profile. It should be noted, however, that pulmonary fibrosis could complicate the natural history of rheumathoid athritis (23), and the incidence of this adverse event could be increased by chemotherapetic drugs such as methotrexate (24).

A second patient died for acute brain hemorrage, probably not attributable to EPX administration, since both the coagulation parameters and platelet counts were within normal ranges. Two patients interrupted the chemotherapy treatment due to thrombosis and subsequent removal of the central venous access. It is well recognized that advanced prostate cancer patients have a high incidence of hypercoagulation (25). A pharmacological prophylaxis, therefore, should be considered when planning the positioning of a central venous catheter in this patient population (26).

The remaining 2 causes of treatment withdrawal were performance status deterioration, due to prolonged grade 3 oral mucositis in the already-mentioned patient, who received concomitant radiation therapy on the cervical column, and the occurrence of grade 3 hepatic toxicity in the patient with a history of chronic hepatitis. Five patients attained a PSA response that lasted in 2 of them. This response rate should be noted for this patient series, which was already pre-treated with chemotherapy and/or steroids.

In conclusion, prolonged EPX infusion is feasible and potentially active in the treatment of advanced prostate cancer patients with hormone-refractory disease. Our data confirm the hypothesis that the mode of administration could change the drug toxicity profile (27). Some expected toxicities in fact, such as leukopenia and alopecia, appeared to be significantly reduced with continuous infusion. In contrast, continuous infusion could potentiate the tissue toxicity of radiation therapy and could induce serious hepatic damage in patients with hepatic disease. Lung fibrosis could be an additional serious event that may

occasionally complicate this treatment modality. The positioning of an implantable central venous device in advanced prostate cancer patients requires adequate antithrombosis prophylaxis (25, 26). All these considerations should be carefully taken into account when planning future prospective phase II trials with EPX continuous infusion in this patient population.

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