

No Additional Benefit of Adding Ifosfamide to Docetaxel in Castration-resistant Metastatic Prostate Cancer

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Abstract. *Background:* In the treatment of many types of cancer, combination chemotherapy has been shown to be better than single-agent chemotherapy. The aim of our phase I-II clinical trial was to assess the efficacy and toxicity of docetaxel-ifosfamide combination chemotherapy in patients with castration-resistant metastatic prostate cancer (CRPC). *Patients and Methods:* A total of 31 patients were enrolled to receive first-line chemotherapy consisting of 40-60 mg/m² docetaxel followed by 3.0 g/m² ifosfamide with mesna. All drugs were administered intravenously. The maximum duration of the chemotherapy was six cycles. The median age of the patients was 70 (range 58-82) years. Prostate specific antigen (PSA) responses were determined according to the PSA working group guidelines and all toxicities, time-to-progression and overall survival were determined according to the WHO criteria. *Results:* The objective PSA response rate was 32% in 11/31 patients. The mean PSA value at baseline was 300 (range 2.5-1577) µg/l. The overall median survival was 14.1 months; 15 patients were alive at a median follow-up time of 18 months. The observed side-effects were as expected, with grade 3-4 neutropenia developing in 38% of the cycles, whereas febrile neutropenia occurred in only 12% of the patients. The median number of administered cycles was 4.8. No acute hypersensitivity reactions were observed. Transient renal insufficiency developed in two patients, thus necessitating dose reductions. *Conclusion:* The combination of docetaxel and ifosfamide seems to be well-tolerated and has some activity in patients with CRPC. However, newer docetaxel-based combination chemotherapy regimens need to be further developed in order to provide more efficacious and well-tolerated treatment options for earlier phases of CRPC.

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Castration-resistant prostate cancer (CRPC) often presents with a clinical picture of multiple bone metastases, a deteriorating overall performance and a life expectancy of approximately 12 months (1, 2). This stage of the disease is frequently preceded by a transient but positive response to hormonal therapy. Taxane-based chemotherapy plays a key role in the treatment of CRPC (3, 4). The majority of patients who initially respond to chemotherapy become resistant and then enter a chemotherapy-resistant final stage.

Docetaxel is a semisynthetic taxoid that is widely indicated for use in the adjuvant and metastatic settings in the treatment of malignancies such as breast (5-7), lung (8-10) and ovarian cancer (11-13). A significant antineoplastic activity with an overall survival benefit with docetaxel-prednisone or docetaxel and estramustine, compared to mitoxantrone and prednisone in CRPC was demonstrated in two large randomized multicenter phase III studies (3, 4). As a result of these studies, docetaxel at 75 mg/m² is accepted as the drug of choice for the first-line, single-agent treatment of CRPC.

Docetaxel-based combinations with other chemotherapeutic agents such as vinorelbine, carboplatin and calcitriol have been studied, with promising results (14-16). The synergistic *in vivo* antineoplastic action of two or more chemotherapeutic agents administered at well-tolerated doses is essential for further improvement in results. Furthermore, the toxicity profiles of the combined drugs must be well-documented to avoid any unexpected additive or cumulative toxicities.

The major dose-limiting toxicity of docetaxel is dose-dependent and is typically transient neutropenia; other toxicities include alopecia, gastrointestinal symptoms, asthenia, hypersensitivity reactions, skin reactions, nail discoloration, sensory neuropathy and fluid retention (17-19). The docetaxel administration schedule is currently under intensive study to further reduce the level of toxicities without compromising its antineoplastic activity (20).

Ifosfamide is an alkylating agent with an antineoplastic effect against multiple solid tumor types, including non-small cell lung, testicular and breast cancer and sarcoma (21-23). The toxicity profile of ifosfamide involves mainly dose-dependent and transient urotoxicity, nephrotoxicity, neurotoxicity, myelosuppression, nausea and alopecia.

Standard single-agent doses range between 5 and 10 g/m², administered as a 24-hour infusion in most cases (25-27).

The majority of patients entering the castration-resistant stage of the prostate cancer face have a greatly limited life expectancy, and most experience a decrease in their quality of life due to fatigue, asthenia, anemia, cachexia, pain and bone-related events such as pathological fractures (1,2). The most important goal of treatment in CRPC remains palliation of symptomatic patients and postponement of the often inevitable decline in the quality of life. The majority of patients who are diagnosed with CRPC are elderly and often present with other chronic systemic diseases, such as diabetes mellitus; therefore, a better-tolerated, safer and more effective combination chemotherapy regimen is required.

Docetaxel and ifosfamide differ in their mechanisms of antineoplastic action and toxicity profiles; therefore, this phase I dose escalation study was continued as a phase II combination study in the treatment of CRPC. The pharmacokinetic interactions of docetaxel and ifosfamide have been previously studied. When docetaxel was administered to patients with advanced solid tumors at a higher dose (85 mg/m²) in a 1-h infusion immediately followed by ifosfamide in a 24-h infusion (5 g/m²), no pharmacokinetic interactions between docetaxel and ifosfamide were observed (8). Furthermore, the clearance of docetaxel was not modified by the co-administration of ifosfamide, even though docetaxel is metabolized by cytochrome 3A4 (CYP3A4) (28) and ifosfamide is metabolized by CYP3A and CYP2B (29). Because docetaxel is now widely accepted as a standard of care in this setting, it is clear that not all patients respond to treatment with docetaxel alone or stated otherwise, become resistant to chemotherapy. Thus, it becomes vital to develop suitable combination therapies and options for second-line palliative treatment for patients with favorable performance status.

Patients and Methods

This was a non-randomized, phase I-II study. Docetaxel-ifosfamide combination chemotherapy was administered to 31 eligible patients. The requirements for participation were CRPC with documented metastasis, a confirmed rising (PSA) in two separate measurements during androgen ablation (either with castration or with luteinizing hormone-releasing analogue), an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, and written informed consent.

Other inclusion criteria were the following: adequate renal function (serum creatinine <2 × normal) and adequate hepatic function (alanine aminotransferase <2 × normal) at baseline, no other serious illnesses and an estimated life expectancy of at least 6 months. Patients' characteristics such as previous treatment, sites of metastasis, significant co-morbidities and duration of response to hormonal treatment are presented in Table I.

Treatment schedule. Chemotherapy was administered in an in-patient setting due to the 24-h ifosfamide infusion. Adequate renal

Table I. *Patients' characteristics.*

Mean age at diagnosis, years	66.9 (range 55-80) years
Mean age at treatment, years	70.2 (range 58-82) years
Prior orchiectomy, n (%)	5 (16.1)
Prior LHRH treatment, n (%)	25 (83.3)
Prior anti-androgen treatment n, (%)	24 (77.4)
Median duration of anti-androgen treatment, months 34.6 (range 2-90)	
0 to 12 months, n (%)	11 (36%)
12 to 24 months, n (%)	4 (13%)
Longer than 24 months, n (%)	16 (51%)
Prior estramustine treatment, n (%)	6 (19%)
Prior radiation therapy of prostate, n (%)	3 (9%)
Prior palliative radiation therapy of bone, n (%)	16 (51%)
Analgesics: use of opiates at baseline, n (%)	6 (19%)
Use of other medication for pain relief, n (%)	21 (68%)
Bone metastasis, n (%)	30 (97%)
Other metastasis, n (%)	4 (13%)

function was determined by creatinine clearance measurements before every cycle. Docetaxel was administered as a 1-h infusion with routine premedication of oral dexamethasone . The treatment was repeated every three weeks for a maximum of six cycles.

Dose modifications. The starting dose of docetaxel was 40 mg/m² and was increased to 50 and 60 mg/m² after a minimum of three patients had tolerated the previous dose. In cases of any grade 3-4 hematological or non-hematological toxicities, the dose was reduced to the previous lower level. The ifosfamide dose was not modified to enable analysis of docetaxel-induced toxicity. Toxicities were evaluated according to the NCI Common Toxicity Criteria.

Criteria for response. PSA responses were based on the PSA Working Group guidelines. Complete response was defined as normalization of PSA; a partial response was defined as at least a 50% decrease from baseline; stable disease was defined as a decrease of less than 50% or an increase of less than 25%; and progression was defined as an increase of more than 25%. All responses were confirmed by a secondary measurement.

Statistical analysis. This was a non-randomized phase I-II dose-finding study. All patients who underwent at least one cycle of chemotherapy were included in the toxicity analyses, and all patients were included in the overall response rate and survival calculations. Overall survival was defined as the time between the first treatment and death; the time to progression was defined as the time between the first treatment and either PSA progression or another objective marker of progression of disease, the end of follow-up or the start of other antitumor treatment.

Results

Baseline patients' characteristics are presented in Table I. The patients had a median age of 67 years and a median performance status of 1 (ECOG scale). All patients exhibited progression of disease during androgen therapy, and all but

Table II. Other phase II studies of docetaxel combination therapy.

Author (ref)	Year	No of patients	Treatment	PSA response rate
Safarinejad <i>et al.</i> (32)	2005	42	D + EMP + SURAM	30.5%
Goodin <i>et al.</i> (14)	2005	40	D + VIN + filgrastin	27-39%
Ryan <i>et al.</i> (31)	2005	34	D + Exisulind	38%
Picus <i>et al.</i> (33)	2011	79	D + Bevacizumab + EMP	75%
Zurita <i>et al.</i> (34)	2009	25	D + Sunitinib + Prednisone	56%
Dahut <i>et al.</i> (35)	2004	75	D + Thalidomide	53%

VIN, Vinorelbine; EMP, estramustine phosphate; D, docetaxel; SURAM, suramin.

one had bone metastasis. The median baseline PSA level was 300 (range 2.5-1577) $\mu\text{g/l}$.

A total of 29 patients were treated per protocol. The median time from the start of primary hormonal therapy to castration-resistant disease was 34.6 (range 2-90) months.

The median number of combination chemotherapy cycles was 4.8 (range 1-6).

The most common hematological toxicity that resulted in dose reductions was grade 3-4 neutropenia in 9 (29%) patients and in 38% of the cycles, respectively. Febrile neutropenia occurred in only 4% of cycles. Transient renal insufficiency (grade 3) resulting in a 20% dose reduction of ifosfamide was observed in three cycles in two patients.

After the first cycle of chemotherapy, one patient was diagnosed with acute subdural hematoma that did not coincide with any trauma or thrombocytopenia; this situation necessitated the discontinuation of treatment. Another patient also underwent only one cycle of treatment due to their rapidly deteriorating overall condition and a subsequent need for palliative bone irradiation.

As regards to antitumor activity, ten patients (32%) exhibited a >50% decrease in PSA from the baseline level. The median time to PSA progression was 6.3 months.

The median survival for all patients was 14.1 months, and the median survival for PSA responders was 16.5 months; 15 patients were still alive after a median follow-up of 18 months.

Discussion

The treatment of CRPC has developed rapidly, and prior standard treatment regimens with demonstrated palliative benefit have been appropriately revised in the light of recent results from docetaxel-based chemotherapy trials (3, 4).

Although a higher percentage of patients now respond to novel treatment strategies and the often inevitable disease progression is postponed, there is still a growing need for a better-tolerated combination chemotherapy regimen that is suitable for older, more fragile patients with chronic comorbidities that limit the use of standard doses of docetaxel.

The increase in antitumor activity observed with more intensive chemotherapy appears to cause unacceptable toxicity and morbidity in these patients. The fatigue and neutropenia associated with docetaxel as well as the renal insufficiency associated with ifosfamide are dose-limiting and dose-dependent.

The results of this study are comparable to those of the other phase II chemotherapy studies in CRPC, presented in Table II (14, 30-35). The study treatment was well-tolerated and anti-tumor efficacy was notable. There was a low incidence of drug-associated toxicity leading to treatment discontinuation. The response to hormonal manipulations after the primary diagnosis was limited; disease in 49% of patients had progressed during the first 24 months and 36% had developed a castration-resistant stage of the disease within the first 12 months of hormonal treatment.

The patient population in this study was best characterized by a short response to hormonal therapy, symptomatic disease requiring analgesic medication and radiotherapy and a very high median baseline PSA level compared to the baseline PSA level of 108-114 $\mu\text{g/ml}$ in the TAX 327 study (3) and to the 84-90 $\mu\text{g/ml}$ level in the SWOG trial (4).

Patients in the TAX 327 study were required to have stable levels of pain for at least seven days before randomization, and 45% had pain at baseline. More than half 16/31 (51.6%) of our study population were treated with palliative radiation therapy for bone pain prior to study treatment; 19% had analgesic opioid treatment at baseline, and 68% experienced pain at baseline. These characteristics are typical of the patient population in normal clinical practice and underline the need for well-tolerated therapy. Novel combination therapies including sunitinib and bevacizumab, although well-tolerated, have not shown significant additional benefit. Compared to the patient population in the two largest randomized trials, our study patient population had more advanced disease. The treatment was well-tolerated and can be used in different types of combinations in the future, as our results are comparable to those of other phase II studies that investigated alternative chemotherapy agents.

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