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Docetaxel plus prednisone in patients with metastatic hormone-refractory prostate cancer: an Italian clinical experience

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Abstract. – *Aims and Background:* **We investigated the efficacy of docetaxel plus prednisone in Italian patients with metastatic hormone-refractory prostate cancer (mHRPC).**

Methods: **Twenty four patients with mHRPC received docetaxel 75 mg/m² every 3 weeks plus prednisone 5 mg twice daily for up to six cycles. The primary endpoint was efficacy measured by a reduction in serum prostate specific antigen (PSA) levels and measurable disease. Evaluation of toxicity, quality of life and reduction of pain were secondary endpoints.**

Results: **PSA response was seen in 18 patients (75%). We observed a partial response in 2 patients (8.3%), stable disease in 10 patients (41.7%), and disease progression in 12 patients (50%). Severe neutropenia was reported in 12.5% of patients.**

Conclusions: **Treatment with docetaxel every three weeks is an effective and well tolerated therapeutic option in patients with mHRPC.**

Key Words:

Adenocarcinoma, Antineoplastic combined chemotherapy protocols, Docetaxel, Drug-resistance, Neoplasm, Prednisone, Prostatic neoplasms, Taxoids.

Introduction

In Western countries, prostate cancer is the second leading cause of cancer-related death in men[1]. The prevalence of both histological and clinical disease increases with age. Forty percent of men over 50 years of age manifest the disease histologically, but only 10% will develop clinical symptoms and 1 in 14 will die of a prostate-cancer related event[2].

The therapeutic approaches to androgen-independent prostate cancer[3,4] (also known as hormone-refractory prostate cancer [HRPC]) over the last two decades have been largely unsatisfactory. In an analysis of 26 clinical trials published between 1987 and 1991, rates of objective response were not above 8.7%[5]. The demonstration, during the nineties, that a decline in serum levels of prostate-specific antigen (PSA) was associated with prolonged survival led to the use of PSA levels as a surrogate endpoint in the evaluation of treatment efficacy[6]. At the same time, the assessment of pain intensity and other parameters, including the use of analgesic medications, performance status and quality of life (QoL), were improved and standardized. A number of studies conducted in HRPC patients with few disease-associated symptoms, demonstrated that mitoxantrone combined with corticosteroids improved symptoms but failed to extend survival[7,8].

Docetaxel has linear pharmacokinetics, is mostly (95%) bound to plasma proteins and is metabolized in the liver. Docetaxel binds to β-tubulin units and functions by stabilizing microtubules, resulting in the arrest of mitosis and in the apoptotic process. In HRPC, docetaxel also opposes the effects of Bcl-2, an anti-apoptotic protein especially overexpressed in prostate cancer cells in response to androgen withdrawal (reviewed by McKeage and Keam[9]).

Phase II trials with docetaxel as a single agent demonstrated its efficacy in pain relief and PSA response (defined as a reduction in serum PSA levels of at least 50%) in up to 50% of patients[10-12]. The efficacy of docetaxel in HPRC was further demonstrated in two pivotal, randomized, multicenter, phase III studies, the TAX 327[13] and Southwest Oncology Group (SWOG) 9916[14] trials. These were the first to show a significant sur-

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vival benefit in patients with HRPC receiving docetaxel plus prednisone[13] or estramustine[14] compared with those receiving mitoxantrone plus prednisone. The overall results of the SWOG 9916 study did not differ significantly from those obtained in the TAX 327 study. In both studies, a higher incidence of adverse events was reported in patients receiving docetaxel. However, most events were not severe[13,14]. Docetaxel administered every three weeks in combination with prednisone was subsequently approved by the United States Food and Drug Administration and the European Medicines Agency as the recommended standard of care for the treatment of HRPC[15].

Of note, an updated survival analysis of TAX 327 data recently confirmed the improved survival benefit (an increase from 2.4 months in the original analysis to 2.9 months) and prolonged median survival duration (19.2 versus 16.3 months) in patients receiving docetaxel every three weeks plus prednisone compared with those in the mitoxantrone group[16]. The Authors concluded that docetaxel administered every three weeks plus prednisone remains the preferred treatment option for most patients with metastatic HRPC (mHRPC).

The present study was designed to further assess the safety and efficacy of the combination docetaxel (Taxotere®) plus prednisone in patients with mHRPC in an Italian setting.

Patients and Methods

Patients

Initially, consecutive patients aged >50 and <70 years old with a diagnosis of mHRPC were recruited in this study. However, part-way during the study, entry criteria were modified to include a small number of patients who did not meet inclusion criterion regarding age, but who met all other inclusion criteria. This was in accordance with the International Society of Geriatric Oncology guidelines that suggest comorbidities are more important than age when deciding whether or not to initiate a therapy. HRPC in our clinical practice is defined as adenocarcinoma of the prostate which had been previously treated with complete or partial androgen blockade followed by addition of an antiandrogen and presenting with three consecutive rises of PSA serum levels two weeks apart, resulting in two 50% increases over nadir, according to the criteria we adopt in our clinical practice. Patients were required to have clinical or radiologic evidence of metastatic disease with ≥1 lesion and the following laboratory findings: neutrophils >2.0 × 10^9/L; platelets >100 × 10^9/L; hemoglobin >10 g/dL; creatinine <1 × the upper limit of normal (ULN); creatinine clearance of >60 mL/min if creatinine was above the limit indicated; bilirubin <1 x ULN; AST and ALT <5 × ULN; and alkaline phosphatase <5 × ULN (unless bone metastases were present). Other inclusion criteria were an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, and compliance and geographical location that permitted follow-up.

Patients were excluded from the study if they were hypersensitive to docetaxel and its excipients, to polysorbate 80 or to other components of the formulation, or in the presence of other malignancies, with the exception of radically excised basal cell carcinoma. Other exclusion criteria included serious comorbidities not adequately controlled by ongoing therapy (e.g. liver disease, diabetes, infection, cardiac disease, etc.). Patients were also excluded if regular follow-up was not possible, if corticosteroids were contraindicated, or if they had other conditions considered by the investigator as risky for the patient or as interfering with study progress. Written informed consent was obtained from all patients prior to beginning treatment and the study was approved by our institutional Ethical Committee in accordance with the international standards of good clinical practice.

Study Design and Treatments

This single-center study was conducted at the Medical Oncology Unit, University of Palermo, Italy, between January 2006 and December 2007. Patients were scheduled to receive docetaxel 75 mg/m^2 by 90-minute intravenous infusion every three weeks plus prednisone 5 mg twice daily in a 6-cycle treatment program. Patients were premedicated with dexametasone sodium phosphate, receiving 8 mg every 12 hours over a 24-hour period (total 24 mg) prior to chemotherapy. After the sixth cycle of docetaxel, patients experiencing a progression could be assigned to restart docetaxel treatment.

Therapy was delayed for up to 2 weeks if neutrophil counts were <1.5 × 10^9/L and/or platelet counts were <100 × 10^9/L, hemoglobin level was <8.5 g/dL, or bilirubin and/or transaminase levels were >1.5 × ULN, according to the common

clinical practice of our center. No reduction of dosage was allowed. If toxicity persisted for more than two weeks the patient was disqualified from the study. Radiotherapy was allowed for those symptomatic lesions considered to be non-evaluable.

Efficacy Assessment

The primary endpoint was the evaluation of response rate in terms of PSA reduction and of measurable pathology at 4 weeks after the end of treatment. Response to treatment was evaluated before each treatment cycle, then every 3 months until disease progression. Evaluation of toxicity, QoL and reduction of pain were secondary endpoints.

In order to define response to therapy (both objective and subjective responses) the following criteria were used for patients with measurable pathology: Response Evaluation Criteria In Solid Tumors (RECIST) criteria[17] (only applied to non-bone metastases); mono- or bi-dimensionally measurable pathology; evaluation criteria of biochemical response (≥50% reduction of PSA confirmed by a second evaluation after 4 or more weeks). A CT-Scan was undertaken on average every 8-10 weeks, always before chemotherapy administration, then every 12 weeks thereafter once chemotherapy was completed. For those patients that did not display a measurable pathology, a reduction of serum levels of PSA ≥50% of baseline values sustained for at least 4 weeks was considered to be a response to treatment. PSA was determined before every cycle of therapy and then every 4 weeks after the end of treatment, but only PSA values after the end of treatment were considered for the evaluation of PSA response.

PSA progression was considered as: a) an increase in PSA values ≥25% of baseline values in those patients who did not experience a significant reduction (≥50%) of serum PSA levels during treatment; b) an increase ≥50% of the lowest level observed in patients who did experience a significant reduction (≥50%) of serum PSA levels during treatment.

All patients also had assessment of ECOG performance status; analgesic therapy; pain measurement test according to the Visual Analog Score (VAS); and QoL according to the Functional Assessment of Cancer Therapy-Prostate (FACT-P). Pain and QoL endpoints were determined at every physical examination (i.e. following each treatment cycle and then every 3 months thereafter).

Toxicity Assessment

Treatment-associated toxicity and adverse events were evaluated at the end of each treatment cycle and reported according to the Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0.

Statistical Analysis

The sample size was estimated based on a minimal PSA response rate from the literature of 25% (P0), considering an alpha error of 5% and a statistical power of 80%. Therefore, according to single-stage phase II designs of Fleming[18], 24 patients were enrolled.

Results

Patient Characteristics

A total of 24 patients aged 45-85 years (mean 65 years) were enrolled and evaluated in this study. The baseline characteristics of these patients are detailed in Table I. Patients completed up to six treatment cycles (median of 5 cycles, range 2-6); treatment was interrupted in six patients due to neutropenia.

Table I. Baseline patient characteristics. Data presented as number of patients unless otherwise stated.

	Patients (n = 24)
Mean age (range), years	65 (45-85)
ECOG performance status	
0	2
1	21
2	1
PPI 2 or AS 10	11
Hormonal manipulations:	
I	4
II	12
III	8
Median PSA level (range), ng/mL	118 (1.2-2057)
Gleason score:	
7	12
8-10	10
Not available	2
Disease extent:	
Bone and visceral metastases	18
Visceral disease	2
Lymph nodes	4

AS, analgesic score; ECOG, Eastern Cooperative Oncology Group; PPI, Present Pain Intensity; PSA, prostate-specific antigen.

Efficacy

The PSA response rate at 4 weeks after the end of treatment was 75% (18 of 24 patients), and the median reduction in PSA levels from baseline was 32 ng/mL.

After a median follow-up duration of 11 months (range 2-21 months), a partial response (PR) to therapy was shown by two patients (8.3%), 10 patients (41.7%) had stable disease (SD) and 12 (50%) showed progression of disease (PD). The median duration of response was 5.2 months (range 3–8 months), and the median time to progression in patients with PR or SD was 6.2 months (95% CI: 4.6-7.8 months). The median overall survival was 15.7 months (95% CI: 11.6-19.8 months).

The response to pain, evaluated according to the VAS pain measurement test, demonstrated a reduction of pain in 14 (58.3%) patients. An improvement in QoL was also shown with pain symptom reduction: 58.3% of patients reported a VAS score of <22 points and a reduction of analgesic use in 54% (13) patients. An improvement in QoL scores of >16 points on the FACT-P score compared with baseline was shown in 32% of patients.

Tolerability

Docetaxel plus prednisone was well tolerated, with only 12.5% patients developing grade 3 neutropenia. Treatment-associated toxicity and adverse events are detailed in Tables II and III, respectively. No patients discontinued treatment due to severe adverse events and only one case of febrile neutropenia was observed.

Table II. Treatment-associated toxicity

Adverse Events of Any Grade	No. of Patients (%)
Hematologic	19 (79.2)
Neurologic	9 (37.5)
Gastrointestinal	6 (25.0)
Infections	4 (16.7)
Metabolic	3 (12.5)
Flu-like symptoms	3 (12.5)
Cardiovascular	2 (8.3)

Discussion

In Western countries, prostate cancer is the most common cancer among men. This study aimed to assess the efficacy of docetaxel plus prednisone in Italian patients with mHRPC. Results presented here demonstrate that treatment with docetaxel plus prednisone is well tolerated and associated with a modest rate of objective response and a good reduction in PSA levels. We acknowledge that many criteria – concerning for instance the response evaluation – are slightly different from international ones, thus limiting the generizability of the findings. However, we speculate that this may reflect the common clinical practice.

In the mid-1990's, Tannock et al demonstrated the benefit of chemotherapy (mitoxantrone plus prednisone compared with prednisone alone) in the palliative treatment of HRPC[8]. The pivotal study, TAX 327[13], showed significantly greater survival rates as well as improved responses in terms of pain, serum PSA levels and QoL in HRPC patients receiving chemotherapy with docetaxel plus prednisone compared with mitoxantrone plus prednisone. Petrylak et al[14] also demonstrated a significant extension of overall survival in patients treated with docetaxel plus estramustine compared with patients receiving mitoxantrone plus prednisone.

The present study enrolled 24 patients with advanced prostate cancer previously treated with hormonal therapies. Treatment with docetaxel plus prednisone was well tolerated and associated with a good rate of disease control (PR + SD; 50%) and a reduction in PSA levels in 75% of patients. Improvement in QoL, a decrease of pain symptoms in

Table III. Adverse events graded according to Common Terminology Criteria for Adverse Events, Version 4.0 (n = 24).

Adverse event	No. of patients (%)
Hematological	
Grade 2-3 anemia	9 (37.5)
Grade 1-2 neutropenia	6 (25.0)
Grade 3 neutropenia	3 (12.5)
Grade 3 thrombocytopenia	1 (4.2)
Febrile neutropenia	1 (4.2)
Nonhematological	
Grade 3 asthenia	8 (33.3)
Grade 2-3 peripheral neuropathy	6 (25.0)
Grade 3 stomatitis	3 (12.5)
Grade 2 alopecia	2 (8.3)
Grade 2 skin reactions	2 (8.3)
Grade 2-3 diarrhea	2 (8.3)

60% of patients and a reduction in analgesic use in 57% of patients was also shown. These results are in accordance with those reported in the TAX 327 study[13], although limitations of this study, which should be taken into account when interpreting the results, include the small sample size, and the difference in the definition of HRPC used in our clinical practice (three consecutive rises of PSA serum levels two weeks apart, resulting in two 50% increases over nadir) compared with recent PSA Working Group criteria (a sequence of rising values of PSA at a minimum of 1-week interval with a level of PSA above 2 ng/ml as a starting value)[19]. Furthermore, after the 6th cycle of docetaxel, some patients experience resistance to, and/or a severe reduction in tolerability of the drug. Therefore, we limited treatment to a maximum of six docetaxel cycles, which is fewer than are commonly used (up to 10 cycles) in the treatment of disease progression. However, after the sixth docetaxel cycle, patients experiencing a progression after treatment could be assigned to restart docetaxel therapy, as second-line therapeutic options are limited[20,21].

The results from the current study are also similar to those presented by Petrylak et al.[14], who showed that the median time to progression (progression-free survival) was significantly increased in patients receiving docetaxel plus estramustine compared with those receiving mitoxantrone plus prednisone (6.3 vs. 3.2 months; $p<0.001$).

More recently, the efficacy of docetaxel plus prednisone has been investigated in both Western and Eastern countries. The Taxotere in Prostate Cancer (TIPC) study[22], conducted by the Norwegian Urological Cancer Group (closed for patient entry in December 2004), demonstrated that weekly administration of docetaxel plus prednisolone compared with prednisolone alone was associated with a ≥50% PSA reduction from baseline at week 6 in 54% versus 26% of patients, a mean progression-free survival of 11 versus 4 months, as well as superior pain relief and QoL. Chinese patients with HRPC showed a higher average time to PSA progression (37.8 versus 25.3 weeks) following administration of docetaxel plus prednisone compared with mitoxantrone plus prednisone[23], and a retrospective study showed that docetaxel every three weeks plus prednisone was associated with a higher rate of PSA reduction compared with weekly docetaxel (69% vs 53% of patients), a prolonged median time to progression (8.5 vs 3.5 months), and an improved survival rate[24].

A number of studies have investigated the use of docetaxel as second-line chemotherapy in patients with HRPC. Joshua et al.[25] reported that weekly docetaxel was a safe and active second-line treatment after mitoxantrone in patients with HRPC. More recently, a study investigating the use of docetaxel every three weeks plus prednisone in patients with HRPC who had progressed on or after first-line treatment with mitoxantrone/prednisone demonstrated a PSA response in 57% of patients and a median progression-free survival of 5 months[26]. A significant and sustained reduction in pain was reported in 75% of patients, analgesic scores were reduced in 78% of patients and the median overall survival was 15 months. Of note, non-hematological toxicity was similar to that reported by Tannock et al[13]. However, the incidence of febrile neutropenia and toxic death were slightly increased. The Authors concluded that docetaxel as second-line chemotherapy may be a beneficial therapeutic option in selected patients with HRPC previously treated with mitoxantrone[26].

Neutropenia is the most frequent adverse event associated with docetaxel[27]. In the present study treatment with docetaxel was well tolerated with only 12.5% of patients developing severe neutropenia (CTCAE Grade 3). This finding is in agreement with published data showing an increased risk of mild-to-moderate adverse events associated with docetaxel treatment[13,14,23].

Conclusions

Our results, although from a limited number of patients, are in agreement with the clinical evidence reported in the literature. Docetaxel is effective, well tolerated and safe in patients with mHRPC, and the treatment-associated toxicity is acceptable. Pain response rates are satisfactory, given the fact that they are attained in patients with progressive HRPC despite several previous courses of hormonal therapy. Based on these findings, we conclude that treatment with docetaxel every three weeks is a valuable therapeutic regimen for progressive prostate cancer.

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