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Original Article

THREE-WEEKLY DOCETAXEL WITH PREDNISOLONE FOR PATIENTS WITH HORMONE-REFRACTORY METASTATIC PROSTATE CANCER: PRELIMINARY RESULTS

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ABSTRACT

Background: The aim of this phase II clinical study was to evaluate three -weekly docetaxel plus prednisolone as first-line chemotherapy for treatment of hormone-refractory metastatic prostate cancer (HRMPC).
Materials and Methods: Thirty five metastatic HRPC patients were treated with docetaxel 70 mg/m2 on Day 1, every 3 weeks plus oral prednisolone 5 mg twice daily at Clinical Oncology Departments, Tanta, Mansoura and Menofia University Hospitals during the period from June 2006 to December 2008. The primary endpoint was assessment of the overall tumor response rate. Secondary endpoints were assessment of PSA response rate, overall survival rate and the time to disease progression.
Results: In 35 patients with metastatic HRPC, the median number of cycles administered was 6 cycles. Partial response was observed in 15 patients (42.9%) with evaluable measurable disease. Median survival from protocol entry was 12 months. Median time to disease progression was 9 months. Prostate-specific antigen (PSA) declined ≥50% in 9 patients (25.7%). The most common grade 34/ toxicity associated with studied protocol was neutropenia (85.7%).
Conclusions: When given with prednisolone, treatment with docetaxel every three weeks lead to improved survival and response rates with accepted tolerability.

Key Words: prostate cancer, hormone, refractory, docetaxel, prednisone, chemotherapy.

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INTRODUCTION

Prostate cancer is the most frequently diagnosed cancer in men with an estimated 192,280 new cases and 27,360 deaths of prostate cancer will occur in the US during 2009[1].

However, approximately 22% of cases will be diagnosed with advanced or metastatic disease, with an additional 25% developing metastases throughout the course of the disease. The majority of prostate cancers initially respond to hormone therapy, with median response duration in metastatic disease of around 18 months. However, in most patients the cancer will become resistant to hormonal treatment and will progress. After developing hormone-resistant disease, survival is not expected to exceed 9–12 months. Treatment for HRMPC is palliative[2]. The options then include symptomatic care with narcotic analgesics, radiotherapy to dominant sites of bone pain, treatment with bone-seeking isotopes such as strontium-89 and cytotoxic chemotherapy[3].

Prostate cancer was considered resistant to chemotherapy until the mid-1990s, when mitoxantrone with prednisone (MP) was shown in a Canadian study to have a role in the palliative treatment of HRMPC.[2] Men with HRMPC experienced an improvement in pain and QOL if treated with MP compared with prednisone alone. No survival benefit was detected in trials comparing mitoxantrone plus corticosteroids with corticosteroids alone, although the studies were not powered to detect small differences in survival[4,5].

In 2004, reports of the TAX 327 and Southwest Oncology Group 99-16 studies showed significant survival benefit when docetaxel-based treatment was compared with mitoxantrone for men with HRMPC[6,7]. In 2007 Shimazui et al through a retrospective Japanese study had concluded that, a regimen of 70 mg/m2 of docetaxel every 3 weeks and 10 mg/day of prednisolone given orally had a favorable outcome with high rate of PSA reduction and an acceptable number of adverse events[8].

Docetaxel, a semi-synthetic taxoid, disrupts the cellular microtubular network, promoting assembly of stable microtubules and inhibiting disassembly. The recommended dose of docetaxel for phase II trials was 70 mg/m2 in minimally pretreated patients[9]. Docetaxel was approved by the US Food and Drug Administration and is currently a promising treatment for patients with HRMPC.

Since 2004 and the first improvement in overall survival in HRMPC brought about by docetaxel, numerous phase II and III studies have been initiated. Considering the lack of efficacy in terms of overall survival, hormonal manipulations such as antiandrogen withdrawal, diethylstilb-esterol or

dexamethason are only indicated in patients with "rising PSA" without clinical or radiological evidence of metastases. As first line treatment, the optimal chemotherapy regimen is docetaxel (75 mg/m2 every 3 weeks) in association with prednisone (5 mg twice daily). Second line chemotherapies (mitoxantron, ixabepilon, docetaxel as a re-treatment, vinorelbin, doxorubicin) provide modest results only in terms of progression-free survival[10].

Bisphosphonates, particularly zoledronic acid, has been shown to have an anti-tumoral synergistic interaction with taxanes both in-vitro and in-vivo[11,12]. Moreover, bisphosphonates may reduce skeletal-related events, besides reducing pain and analgesic requirement. Therefore the combined use of zoledronic acid with docetaxel and prednisone is being tried for its possible survival benefit and improvement of quality of life[13]. One pilot report using this combination showed significant improvement in pain and reduction in analgesic requirement with a reduction in PSA by more than half in more than 50% of patients[14].

MATERIALS AND METHODS

Materials:

This prospective, phase II multi centre study included 35 patients with HRPMC. Those patients had been treated inclusively by a regimen of docetaxel and predenisone at Clinical Oncology Departments, Tanta, Mansoura and Menofia University Hospitals during the period from June 2006 to December 2008. The age of the patients ranged from 52 to 73 years, with the mean age of 65.3 ±5.14 years.

Patient Selection:

Eligibility criteria included histologically proven metastatic adenocarcinoma of the prostate with progressive disease, despite androgen deprivation. Disease progression for HRPC patients was defined as appearance of new lesion(s) and/or an increase of >25% of measurable metastases and/or the appearance of new foci on a radionuclide bone scan and/or three consecutive increases in PSA concentration at least 1 week apart in the presence of testosterone castrate level of metastatic patients.

Other eligibility criteria included no prior chemotherapy, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2 and at least 4 weeks since completion of radiation. Antiandrogen withdrawal and subsequent documented disease progression was required before study entry (at least 4 weeks since prior flutamide, cyprotrone acetate or baclutamide and 6 weeks since prior bicalutamide). Patients were required to have a castrated level of testosterone (< 50 ng/mL) achieved by bilateral orchidectomy or administration of luteinizing-hormone releasing hormone agonist. Patients were excluded for uncontrolled diabetes and all comorbid conditions that may limit survival. Patients' written consent was obtained in every case.

Radiological investigations, including radionuclide bone scan, computed tomography scan of the abdomen and pelvis and chest x-ray were performed pre-treatment as baseline and at a minimum every 12 weeks. Physical examinations and laboratory studies included CBC, serum chemistry profile, testosterone and PSA were performed pre-treatment and at a minimum every 4 weeks.

Patients were required to meet the following hematological criteria prior to commencement of each treatment cycle: neutrophil count >2000 µl; hemoglobin above 10 g/dl and a platelet count above 100 x 103/µl; total serum bilirubin of ≤ 1.5 times of institutional upper limit of normal level (ULN); aspartate and alanine aminotransferase levels ≤1.5 times ULN; creatinine levels ≤1.5 times ULN; alkaline phosphatase less than 2 times ULN.

Treatment:

Patients received docetaxel 70 mg/m2 administered as ≥1-h intravenous infusion on Day 1, every 3 weeks plus oral prednisolone 5 mg twice daily starting on Day 1 and continuing throughout treatment. Treatment was planned for 10 cycles; for those patients who had a continued clinical benefit beyond 10 cycles, entry into a separate clinical study of extended therapy was permitted. Patients continued to receive prednisolone in the event of withdrawal from the study and after completion. In the event of prednisolone discontinuation, the dose was tapered to avoid withdrawal syndrome. The dose of docetaxel was reduced by 10 mg/m2 in subsequent treatment cycles if any of the following criteria were met: 3/4 grade hematological toxicity, thrombocytopenia; or grade 3/4 non-hematological toxicity (including neurotoxicity, nausea and/or vomiting, infection or allergic reaction). Dose reduction or cessation of prednisolone administration was considered in cases of peptic ulcer, posterior subcapsular cataract, glaucoma and infection. Patients were removed from protocol therapy for a treatment delay greater than 3 weeks or recurrence of the same grade ≥ 3 toxicities despite of 2 dose reductions. However treatment continued until disease progression occurred. Granulocyte colony-stimulating factor (G-CSF) could be administered during any cycle in which the neutrophil count was <1000 x106 cells/l in the presence of fever (≥38.8C) or, <500 x 106 cells/l in the absence of fever. Prophylactic anti-emetics, antihistamines and corticosteroids could be administered if required. Patients who progressed after at least 2 cycles of protocol treatment or who stopped treatment for toxicity or other medical reasons were eligible to receive the alternate treatment.

Assessments:

The primary endpoint was the overall tumor response rate, assessed with WHO guidelines[15]. Overall tumor response (measured by visceral and/or soft-tissue assessment, primary prostate lesion assessment and bone scan) was assessed at cycles 2, 6 and 10 and to confirm response.

Secondary endpoints were PSA response rate, overall survival rate, the time to disease progression and assessment of pretreatment prognostic factors. PSA decline (≥50%) was documented in accordance with the consensus guidelines of

the PSA Working Group[16]. The time to PSA progression was measured from the date of start of treatment to the date of PSA progression and was defined by a ≥ 25% increase in PSA level from baseline or a ≥50% increase in PSA level from the lowest value achieved, provided that the increase was at least 5 ng/mL, confirmed by three successive measurements at 3-week intervals. The duration of PSA response was the time interval between the dates of the first 50% decline in PSA until PSA increased to 50% above the nadir. Overall survival was defined as the time between study entry and death or date of last follow-up. Treatment toxcicties were collected from the first administration of docetaxel through to 6 weeks from the last administration of docetaxel and were evaluated according to The Common Toxicity Criteria (CTC)[17].

Statistical Analysis:

This phase II study was planned to accrue a total of 35 patients. Data was manipulated using the SPSS 10 statistics database Patient's characteristics were summarized by descriptive statistics (median, range and frequency).The percentage of patients experiencing clinical response (PR) was reported along with the corresponding exact 95% confidence intervals (CI)[18]. Kaplan–Meier curves[19] (with 95% CI) were plotted for OS and PFS. Univariate analysis of pre-treatment factors and treatment response on median time to disease progression and median overall survival was performed and statistical significance assessed by the log-rank test. The p value of ≤0.05 was considered significant.

RESULTS

Patient baseline characteristics are detailed in Table (1). A total of 202 cycles of treatment were administered to 35 patients (median 6 cycles per patient (range 2–10)) as first-line treatment. Eighty five percent of patients received at least 5 cycles of therapy.

The overall tumor response rate (PR plus SD) was 74.3% (95% CI equal 57.95 to 85.85); all responses were partial responses (PR) as none of studied patients had achieved complete response. Stable disease was observed in 11 patients (31.4%). The disease had been progressed in 9 patients (25.7%) with a median duration of response was 16.2 weeks as shown in Table (2).

PSA response was seen in 24 (68.6%) of patients, with ≥50% reduction of the baseline level had occurred in 9 (25.7%) patients and <50% reduction of the baseline level had occurred in 15(42.9%) patients. The median duration of PSA response was 16 weeks. PSA level had progressed in 11 (31.4%) and the median time to PSA progression was 20.4 weeks. as shown in Table (3).

The median overall survival time for all patients was 12 months (with 95% CI equal 10.51 to 13.49 and Standard Error equal 0.76) as shown in table 3 and figure 1. The median time to disease progression for all patients was 9 months (with 95% CI equal 8.1 to 9.9 and Standard Error equal 0.76) and mean time was 8.4 months as shown in Table (3) and Figure (2).

A univariate analysis of pretreatment factors (including age, the initial serum PSA levels, the GS, the number of bone metastases and the type of metastases) and treatment response that influence the median overall survival was done as shown in Table(4).

Both hematological and non-hematological toxicities were reported for all 35 patients (100%) and are recorded in Table (5). The most common grade 3/4 hematological toxicities were neutropenia (85.7%), four patients (11.4%) developed grade 3/4 anemia while grade 3/4 thrombocytopenia was not recorded. Five patients (14.3%) developed febrile neutropenia and infection (chest infection) and were treated with antibiotics, growth factors and antipyretics.

The most common grade 3/4 non-hematological event was sensory neuropathy (11.4%) followed with alopecia (8.6%), nausea and/or vomiting (5.7%) and infection without neutropenia (5.7%). Grade I and II edema occurred in 4/35 (11.4%) patients. Adverse events that led to the discontinuation of treatment included sensory neuropathy and infection. No treatment-related deaths were recorded.

Table 1: Baseline characteristics of patients with HRMPC.

	No (35)	%
Age in years		
< 60		
61-70		
>70	5	14.3
Range 52-73	22	62.9
Mean 65.3	8	22.8
Median 65		
Std. Deviation ± 5.14		
PSA		
<50 ng/Ml	14	40
>50 ng/Ml	21	60
Range 20.0 - 2148.0 ng/Ml		
Mean 331.3 ng/ Ml		
Performance status		
I	18	51.4
II	17	48.6
Gleason Score		
2-4	1	2.9
5-7	14	40.0
8-10	20	57.1
Metastatic sites		
Bone only	26	74.3
Bone and soft tissue	9	25.7
Number of bone mets		
<6	13	37.1
>6	22	62.9
Time since diagnosis of MPC		
1-2 year	14	40.0
>2-3 years	17	48.6
> 3 years	4	11.4
Previous treatment		
Casteration + flutamide Casteration +	18	51.43
Cyproterone acetate	11	31.43
Goserelin + fluamide	2	5.71
Goserelin + biclutamide	4	11.43

mets: metastases, MPC: metastatic prostate cancer.

Table 2: Best overall tumor response by WHO response criteria (primary endpoint).

Response	No	%
CR	0	0.00
PR	15	42.9
SD	11	31.4
Progressive disease	9	25.7
Overall tumor response (PR+SD) (95% CI)	26	74.3
	57.95 to 85.85	

Table 3: Secondary end points.

Secondary end points		95% confidence Interval	Standard Error
PSA response n (%)			
≥50% reduction	9(25.7)		
<50% reduction	15(42.9)	14.2 – 42.1	
Progressive elevated	11(31.4)		
Overall survival (months)			
Range	4-24		
Median	12	10.5-13.5	0.76
Mean	12.9	11.5-16.70	1.34
Time to DP (months)			
Range	2-14		
Median	9	8.10-9.90	0.46
Mean	8.9	7.81-10.12	0.59

DP: disease progression.

Table 4: A univariate analysis of pre-treatment factors and treatment response on median time to disease progression and median overall survival.

Prognostic variables	No. (%)	Median Time to disease progression (Months)	p value	Median overall survival	p value
Age in years					
≤ 65	17 (48.6)	10	0.24	19	0.35
> 65	18 (51.4)	8		14	
Performance status					
I	18 (51.4)	10	0.053	20	0.13
II	17 (48.6)	9		10	
Initial PSA level					
≤50ng/ml	14 (40)	10	0.28	19	0.22
>50 ng/ml	21 (60)	8		14	
Gleason score					
≤7	15 (42.9)	10	0.07	20	0.27
> 7	20 (57.1)	8		15	
Bone metastases					
<6	13 (37.1)	10	0.69	18	0.87
≥ 6	22 (62.9)	8		14	
Metastatic sites					
Bone only	26 (66.7)	9	0.43	16	0.38
Bone & soft tissue	9 (33.3)	10		10	
Treatment response					
PR [a]	15 (42.9)	11	0.28 (a vs. b)	22	0.008(a vs. b)
SD [b]	11(31.4)	9	0.006 (b vs. c)	14	0.059 (b vs. c)
Progressive disease [c]	9 (25.7)	2	0.00001(a vs. c)	8	0.0001(a vs. c)

P ≤0.05 is considered significant. vs.: versus.

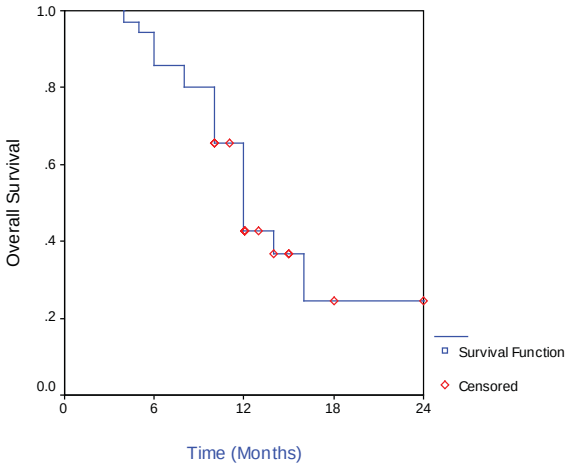

Figure 1: Overall survival of all patients.

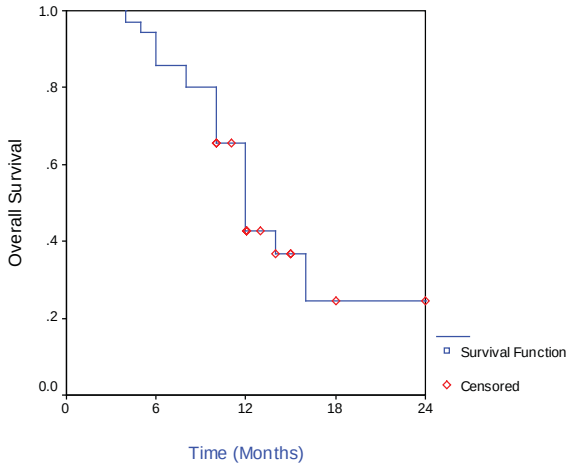

Figure 2: Progression free survival of all patients.

Table 5: Treatment-related adverse events.

	Any grade		Grade 3-4	
	No	%	No	%
Neutropenia	34	97.1	30	85.7
Anemia	29	82.9	4	11.4
Thrombocytopenia	7	20.0	0	0
Alopecia	22	62.8	3	8.6
Nausea and/or vomiting	15	42.8	2	5.7
Anorexia	7	20.0	0	0.0
Neuropathy	10	28.6	4	11.4
Fatigue	12	34.3	0	0.0
Diarrhea	9	25.7	0	0.0
Infection	5	14.3	2	5.7
Nail toxicity	4	11.4	0	0
Edema	4	11.4	0	0

DISCUSSION

In this study, a schedule of docetaxel on Day 1, every 3 weeks plus oral prednisolone twice daily had been evaluated for patients with hormone-refractory metastatic prostate cancer.

The characteristics of the patients in this study are typical of those seen in oncology practices. Most patients were elderly and had received at least two types of hormonal treatment. Most had bone metastases and a high serum PSA level and all these patients had a short life expectancy.

Historically, prostate cancer has been considered to be a chemo-resistant disease with earlier trials showing disappointing response rates (<20%). However, in 1996 Tannock et al published their randomized study revealing the first evidence of palliative benefit of mitoxantrone and prednisolone over prednisolone alone in patients with symptomatic MHRPC.[4] Subsequent studies confirmed the same results but failed to a show a survival benefit for chemotherapy, until in 2004; two landmark studies (TAX-327and SWOG 99-16) provided the first evidence of survival benefit with docetaxel-based chemotherapy for patients with MHRPC[6,7]. In TAX 327 study, 1006 men with MHRPC received prednisolone 5 mg twice daily and were randomized to receive mitoxantrone 12 mg/m2 every three weeks, docetaxel 75 mg/m2 every three weeks, or docetaxel 30 mg/m2 weekly for five out of every six weeks. This study confirmed superiority of the three-weekly docetaxel regimen over mitoxantrone with a significant improvement in median survival (18.9 vs. 16.5 months; P=0.009), PSA response (45 vs. 32%; P<0.001) and pain response (35 vs. 22%; P=0.01).

Also In the SWOG 99-16 trial, 770 men were randomized to receive either estramustine 280 mg orally three-times daily on Days 1–5 of a 3-week cycle, docetaxel 60 mg/m2 on Day 2 or mitoxantrone 12 mg/m2 on Day 1 plus prednisone 5 mg daily. Median overall survival was significantly longer among patients treated with docetaxel–estramustine compared with those receiving mitoxantrone–prednisone (17.5 versus 15.6 months, respectively; P = 0.02). The median time to progression was 6.3 months for docetaxel–estramustine and 3.2 months in the mitoxantrone–prednisone group. Based on the results of these studies, the National Institute for Health and Clinical Excellence (NICE) committee approved ten cycles of three weekly docetaxel chemotherapy (75 mg per m2) in combination with prednisolone 10 mg daily as standard of care for first-line chemotherapy in patients with HRMPC[20].

The primary endpoint in the present study was overall tumor response rate. The overall tumor response rate (PR + SD) of 74.3% in the present study with no patients had achieved CR. These results compare favorably with that reported with Naito et al.[21] in a phase II Japanese study, included 43 patients with HRMPC, the overall tumor response rate was 76.7%. On the other hands, Zhang et al.[22], had reported tumor response rate of 72.6% (13.6% CR, 29.5% PR, 29.5% SD and 27.4% progressive disease).

The second end points in this study were PSA response, overall survival time and time to disease progression. In our study, the PSA response rate ≥50% reduction of the base line level was 42.9%. As Shimazui et al.[8], had recorded an overall PSA response rate of 68.8%, our results were highly comparable with Naito et al.[21], Tannock et al.[6] (44.4% and 45%, respectively), on the other hands, Saad et al.[23] and Ansari J et al.[24], had recorded a higher response rates (57% and 54%, respectively).

This study included a schedule of docetaxel given every three weeks rather than a lower doses of docetaxel given weekly. Shimazui et al.[8] had reported that, a fifty percent decrease in PSA was observed in 53% of the patients with a median time to progression of 3.5 months and 69% with 8.5 months with docetaxel weekly and docetaxel q3w regimens, respectively.Patients who received docetaxel every 3 week regimen had a significantly better survival rate than those who received docetaxel weekly regimen. Myelosuppression and neuropathy were statistically more frequent in docetaxel every 3 week than in docetaxel weekly regimen. Even TAX 327 trials have not revealed the difference yet by means of direct comparative analyses[6].

In our study the median time to disease progression and the median survival time were 9 and 12 months. respectively. While, Shimazui et al.[8] had reported a median time to disease progression of 8.5 months and median overall survival of 12.5 months, Saad et al.[23] had reported a median progression-free and overall survival of 5 and 15 months, respectively and Ansari J et al.[24]

median treatment-free interval of 24 and median overall survival was 13 months. However, Howard et al.[25], had reported in a Canadian retrospective study that among 161 patients with HRMPC docetaxel and prednisone did not perform as well in terms of median survival, as it was shown to in prior clinical trials (17.22 vs. 18.9 months).

The SWOG 99-16 trial showed a significantly higher PSA response rate after treatment with docetaxel plus estramustine than with mitoxantrone plus prednisone (50 versus 27%, respectively, P:0.001)[2]. In contrast, the combination of docetaxel 60 mg/m2 plus mitoxantrone 8 mg/m2 every 3 weeks produced PSA responses in only 26% of patients[25]. Although it may be possible to achieve even higher responses with combination regimens of docetaxel plus EMP, these benefits would have to be balanced against any increased toxicity[26].

Most of the adverse events observed in our study were predictable and manageable. The incidence of grade 3/4 neutropenia was 85.7%, only 5 of 35 patients (14.3%) had febrile neutropenia. Adverse events required dose reduction in only 18 of 202 cycles (8.9%). The usage of G-CSF occurred in 63 of 202 cycles (31.2%). There were no deaths during the study or within 30 days of the last dose of study medication. Lin et al.[27] reported that long-term adverse effects associated with continuous docetaxel treatment include asthenia, edema, peripheral neuropathy and cytopenia. In the TAX 327 study, while the 3-weekly docetaxel regimen was associated with grade 3/4 neutropenia in only 32% of patients[6], Naito et al.[17] had recorded 93% grade 3/4 neutropenia with 16.3% of patients developed febrile neutropenia, Shimazui et al.[8] had recorded 75% grade 3/4 neutropenia with 12.5% febrile neutropenia and Numata et al.[28] had found 78% grade 3/4 neutropenia and only I patient with febrile neutropenia.

In Conclusion, Our data suggest that docetaxel 70 mg/m2 every 3 weeks and daily oral prednisolone 10 mg, lead to improved survival and response rates with accepted tolerability for patients with HRMPC. On the basis of the promising results and relatively low toxicity profile, the combination of docetaxel and prednisolone may be considered standard treatment for patients with HRPC. Further investigation of this chemotherapy combination is warranted.

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