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Treatment of Hormone Resistance with Docetaxel in Metastatic Prostate Cancer Patients: Results of a Clinical Experience at Omid Hospital, Isfahan, Iran

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Abstract

Background: Metastatic prostate cancer is one of the most important cancers among men worldwide. Androgen ablation therapy can be used in treatment of these patients; however, most will progress to metastatic hormone-refractory prostate cancer. In this regard, docetaxel has been approved to treat metastatic hormone-refractory prostate cancer in the United States. In this study, we aimed to investigate the results of this treatment modality in metastatic prostate cancer patients from Iran.

Methods: We evaluated PSA response and bone pain relief in 18 metastatic prostate cancer patients who underwent treatment with docetaxel at a dose of 75 mg/m^2 intravenously on the first day of treatment. The treatment was repeated every three weeks (6 cycles) along with 10 mg of prednisolone.

Results: Of 18 patients, 39% had >50% decline in PSA levels.There were 16% of the patients with a PSA decline of approximately 30% to 50% of the pre-treatment levels. In addition, 29% of the patients had progressive PSA levels during chemotherapy. Among them, 55% had significant pain relief.

Conclusion: This research showed the effectiveness of docetaxel to decrease PSA levels in metastatic hormone-refractory prostate cancer patients from Iran. Docetaxel was also valuable in alleviation of pain in these patients. However, prospective studies should validate this approach.

Keywords: Docetaxel, Metastatic hormone-refractory prostate cancer, PSA

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Introduction

Prostate cancer is one of the most important cancers among men throughout the world, especially in Europe and United States.[1,2]

Androgen ablation is a highly effective treatment modality for prostate cancer patients that provides considerable disease control of up to 80%.[3] Androgen deprivation therapy (ADT), also named androgen ablation therapy (AAT), is a treatment of

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choice in these patients.[3] However, after a median duration of 18-24 months, most patients will develop progressive disease- castration-resistant prostate cancer (CRPC), metastatic hormone-refractory prostate cancer (MHRPC), or metastatic hormone-resistant prostate cancer which necessitate alternative treatment options.[3] These include hormonal manipulations which contain the addition of anti-androgens, followed by withdrawal, corticosteroids orestrogen.[5] Of note, the response to hormonal therapy is short-lived and mostly does not impact overall survival.[5] Anti-androgen withdrawal response has been documented in up to 25% of patients with HRPC.[6] Response rates between 5% to 30% have been documented using anti-androgens or glucocorticoids as second-line hormonal treatments for CRPC.[6]

Historically, prostate cancer has been regarded to be a chemo-resistant disease with earlier trials showing disappointing response rates (<20%). However, in 1996 Tannock et al. published their randomised study disclosing the first evidence of palliative advantage of mitoxantrone and prednisolone over prednisolone alone in patients with symptomatic MHRPC in the past years.[7,8] Although, following studies verified the identical results but failed to display a survival benefit for chemotherapy.[9]

Docetaxel was approved for the treatment of metastatic androgen-refractory prostate cancer by the US Food and Drug Administration (FDA) in 2004.[10] Approval was mainly based on two randomized trials that showed a longer median survival of approximately 2 months in patients who received docetaxel compared to those treated with mitoxantrone plus prednisone.[10] In the TAX 327 study, 1006 patients with advanced prostate cancer received 5 mg prednisone twice daily plus 12 mg/m^2 mitoxantrone every 3 weeks,75 mg/m^2 docetaxel every 3 weeks, and 30 mg/m^2 docetaxelonce weekly for 5 weeks. Median survival of the patients treated with docetaxel was 18.9 months, while it was 16.5 months in those treated with mitoxantrone.[10] By taking into consideration the results of these studies, the National Institute for Health and Clinical Excellence (NICE) Committee approved 10 cycles of 3-weekly docetaxel chemotherapy (75 mg/m2) in combination with 10 mg prednisolone as standard of care for first-line chemotherapy in patients with MHRPC. Recently, a phase 3 trial has begun of 2-weekly versus 3-weekly docetaxel to treat CRPC.[10-12] Management of patients who initially respond to docetaxel followed by cancer progression after a period of biochemical remission is still not clearly known. In view of the lack of evidence for this category of patients, the NICE committee did not approve docetaxel re-treatment.[9]

Of note, up to 50% of metastatic prostate cancer patients present with pain as their initial symptom of cancer; 75% to 90% of patients experience pain when cancer reaches the advanced stages.[13] A total of 60% to 90% of patients with metastatic bone cancer suffer from bone pain.[14] Cancer-related pain fundamentally reduces overall quality of life (QOL), although its effect can often be relieved by optimal pain management.[15,16] Recognition and management of pain has been an increasingly important aim for physicians in recent years. The simplest example of a pain assessment tool is the widely used Present Pain Intensity (PPI) scale, adopted from the McGill Pain Questionnaire.[17]

In this research, we aimed to investigate the results of docetaxel chemotherapy in CRPC patients in Iran. This study intended to determine whether the treatment efficiency correlated with serum PSA levels, neutrophil counts (CBC), and pain rate (PPI scale). We also inspected the capability of re-treatment with 3-weekly docetaxel chemotherapy (75 mg/m^2) as this has not been previously reported in Iran. To the best of our knowledge, no published articles presented a study on this issue with the methodology and analysis described here.

Materials and Methods

From December 2011 to December 2012, 18 patients with CRPC received intravenous administration of 75 mg/m^2 docetaxelon the first

day of treatment. This treatment was repeated every three weeks along with 10 mg prednisolone administered daily. Androgen suppression with LHRH agonists was continued throughout the duration of chemotherapy. This study was approved by the Ethics Committee of Isfahan University of Medical Sciences. We retrospectively reviewed the patients' documents to evaluate their baseline characteristics, PSA response, and hematological toxicities (Table 1). The patients rated their pain (typically during the preceding 24-hour period) on a 6-point scale (0 = no pain, 1 = mild pain, 2 = discomforting, 3 = distressing, 4 = horrible, 5 =excruciating). The PPI, similar to all frequently used instruments, does not differentiate between cancer-related pain and pain from other reasons.[18]

Based on the results of the Consensus Conference in 1999, a PSA decline of 50% or more is considered to be a valid end-point when reporting response rates in patients with metastatic prostate cancer.[19] More recently, re-analysis of data from the TAX-327 and SWOG99-16 studies has revealed that a PSA decline of 30% or more with treatment is the best surrogate marker for overall survival.[20,21]

In this study, patients with a >50% PSA increase from the pre-treatment level were determined to have refractory disease. Those whose PSA response did not meet the above criteria were considered to have stable disease. Biochemical response could not be examined in patients whose PSA values were >1500 ng/ml. Hematological toxicity was assessed by the Common Toxicity Criteria of the National Cancer Institute (version 3.0).[22]

Table 1. Patients' characteristics.

Median age (years)	72 (55-86)
Median PSA (ng/ml)	180
PSA >20 ng/ml (%)	96
>2 Hormone manipulations (%)	95
Gleason score (%)	
≤7	13
8-10	5
Prior treatment (%)	
Prostatectomy	4
Radiotherapy	14
Site of metastases	
Bone only	18

Results

All patients with MHRPC received with docetaxel chemotherapy along with prednisolone as a 3-weekly regimen. Baseline characteristics of these patients are illustrated in Table 1. The median age of the patients was 72 years and 40% were at least 75 years of age. A total of 43% had metastatic disease and 57% were symptomatic prior to the start of chemotherapy. The median PSA at commencement of chemotherapy was 180 ng/ml

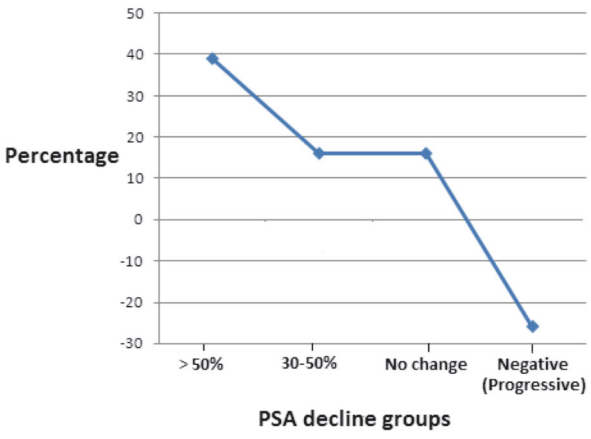

Figure 1. PSA response in patients with metastatic hormone refractory prostate cancer (MHRPC) who received 6 cycles of 3-weekly docetaxel chemotherapy.

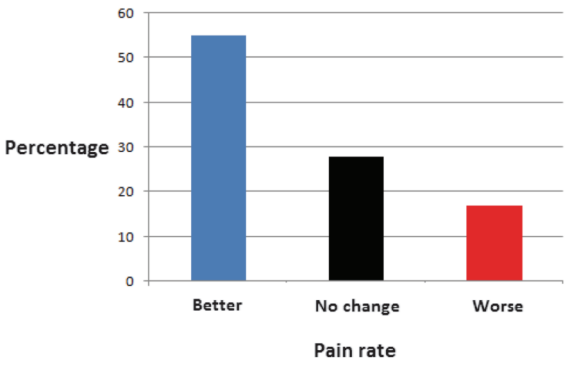

Figure 2. Fraction of patients that experienced significant change in pain evaluated after 6 cycles of treatment with docetaxel. Patients were classified in 3 groups: better (at least a 4-point improvement); worse (at least a 4-point worsening); and no change (a change of less than 4 points).

(range 19.9-1500). Serum PSA measurements were checked at baseline and repeated at 3-week intervals during treatment. There were 18 subjects who completed the planned course of 6 cycles of chemotherapy and qualified to enter this study. From these, 39% had an excellent biochemical response, defined as achieving a PSA falling of >50%. In addition, another 16% had their PSA levels decline between 30% to 50% of the pre-treatment level. There were 16% who had steady PSA measurements, where as another 26% had progressive PSA levels during chemotherapy (Figure 1). Overall incidence of grade 3 or 4 neutropenia was relatively low and affected 17% (n=3) of patients, which impacted only 2.5% of the total number of cycles. Only one patient required hospital admission for management of neutropenic sepsis. There were no treatment-related deaths. Grades 3 or 4 anemia was observed in only 5% of the patients, although 4 (23%) required at least one unit of blood transfusion during treatment. There were no episodes of grades 3 or 4 thrombocytopenia.

This study showed a significant pain reduction in men due to CRPC. A total of 55% of patients met criteria for a significant improvement in pain, whereas 28% met the criteria for stable pain rate, and the remaining palliative responders had significantly worsening pain (Figure 2).

Discussion

Due to advanced radiological investigations and increased frequency of PSA monitoring, the diagnosis of disease progression is being made earlier in patients with MHRPC.[10] Asignificant proportion of these patients will be candidates for second-line chemotherapy, having previously responded to docetaxel and prednisolone as first-line chemotherapy (6 cycles). Not surprisingly, there have been no previous reports of docetaxel re-treatment or intermittent administration using the 3-weekly regimen in patients with MHRPC in Iran.

The role of intermittent versus continuous androgen suppression has been examined in at least three randomized controlled trials.[19-21,23] Although they reported no difference in time to progression or overall survival, of note, the majority of patients achieved normal testosterone levels during the treatment-free period.[23,24] In a similar manner, intermittent administration of chemotherapy has been shown to be an attractive proposition which may offer patients improved QOL during the treatment-free periods.[23,24] Beer et al. prospectively tested intermittent weekly docetaxel and calcitriol in eight patients with HRPC.[25] They found a significant treatment-free interval (nearly 20 weeks) with this approach.[25] Intermittent chemotherapy administration was allowed for patients that achieved a significant biochemical response.[26] Interestingly, of 45 patients who received intermittent chemotherapy, 45.5% showed a biochemical response (PSA reduction >50%) when rechallenged with the same regimen after a median first treatment-free interval of 18 weeks.[25] In our study, we observed a PSA decline of more than 50% in 39% of patients.

New approaches for management of MHRPC are being investigated. However, the majority of these agents are still in early clinical studies. Ixabepilone, an epothilone B analogue has shown modest activity as second-line treatment for docetaxel refractory patients with PSA response rates of <20%.[27] Our research was significantly in line with the above studies and displayed efficient support. However, there is no proof for an effective regimen in this setting. Therefore, patients who respond to first-line docetaxel chemotherapy should be considered for re-treatment. Ansari et al. reported the first evidence that supported docetaxel chemotherapy re-treatment using the 3-weekly schedule in patients with MHRPC.[9] This study clearly demonstrated that patients with MHRPC who initially responded to docetaxel chemotherapy maintained their sensitivity to subsequent retreatment.[9] This could be described by a hypothetical argument that a population of taxane-sensitive cells remained at the end of first-line chemotherapy, which maintained their intrinsic sensitivity and subsequently responded to chemotherapy retreatment.[9]

Pain relief is an important purpose of systemic therapy for CRPC and considered one of the major elements for increased QOL in CRPC patients. Introductory findings suggest that docetaxel is also valuable in the treatment of pain in patients with metastatic prostate cancer.[28,29] Some studies have shown that pain mitigation was achieved in 50% to 60% of patients based on study regimen and number of chemotherapy cycles,[18] which was roughly similar to our results where 55% of patients were in the better group (Figure 2).

As none of the available chemotherapy drugs have shown significant advantage in the better group, the case for docetaxel retreatment becomes stronger in MHRPC patients who initially respond to docetaxel and then progress after a period of biochemical remission. An alternative approach is treatment with intermittent docetaxel chemotherapy for patients with MHRPC, using up to six cycles of chemotherapy as part of first-line chemotherapy (similar to our study) and reserving further cycles for disease progression. However, prospective studies will be needed to validate this approach of intermittent 3-weekly docetaxel chemotherapy with larger numbers of patients. Also, according to certain studies, docetaxel in combination with one of the newer agents will most likely demonstrate better results.[3]

Conflict of Interest:

No conflict of interest is declared.

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