# Efficacy of Taxotere, Thalidomide, and Prednisolone in Patients with Hormone-Resistant Metastatic Prostate Cancer

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**Purpose:** To evaluate the efficacy and safety of combination treatment with thalidomide and taxotere in patients with hormone-resistant prostate cancer.

**Materials and Methods:** This clinical trial was performed on 16 patients with hormone-resistant prostate cancer.

**Results:** Mean age of the participants was 72.7 ± 5.39 years (range, 65 to 85 years). In 94% of patients who received the drug combination, prostate-specific antigen level decreased more than 50%. The mean time to progression was 15 months and mean survival time was 23 months. This combination therapy had some adverse events.

**Conclusion:** Addition of anti-angiogenic agents, such as thalidomide, can improve therapeutic outcome in this group of patients.

**Keywords:** prostatic neoplasms, treatment failure, antineoplastic agents, drug resistance

## INTRODUCTION

Prostate cancer (PCa) is the fifth most common cancer in both genders and the second most common cancer in men. An estimated 900 000 men worldwide were diagnosed with PCa in 2008, accounting for almost one in seven (14%) cancers diagnosed in men (7% of the total in men and women).[1] There have been large increases in the incidence of PCa in many countries worldwide, coupled with little change or small declines in mortality.[2]

Regarding the epidemiology of PCa in Iranian males, the first report from Tehran population-based cancer registry showed that PCa is the second most common cancer in Tehran only after gastric cancer with age-standardized rate (ASR) of 15.6.[3] Based on another report of cancer registry in 5 provinces in Iran, during 5-year follow-up from 1996 to 2000, the ASR of PCa was 5.1 per 100 000 people in a year.[4] The ASR of PCa in Iran shows a slow rise with increasing age.

Hormone therapy in patients with metastatic PCa usually suppresses the disease for a significant period of time, but over the time, most patients will develop progressive disease, which is resistant to hormone therapy.

The appropriate therapy for patients with hormone-resistant PCa is chemotherapy with taxotere-based regimen.[5,6] The mean survival time of patients who received taxotere in combination with prednisolone was 19.2 months, compared to 16.3 months in patients who received mitoxantrone plus prednisolone.[7] Several studies have showed that thalidomide inhibits angiogenesis by inhibiting fibroblast growth factor.[8,9]

Regarding the role of taxotere and thalidomide in metastatic PCa, we decided to evaluate the efficacy of these two medications with different mechanism of action in treatment of hormone-resistant PCa.

## MATERIALS AND METHODS

All recruited patients (16) had advanced metastatic PCa and were symptomatic despite orchiectomy or treatment with GnRH agonists alone or in combination with antiandrogens. A symptomatic or progressive disease was defined based on Prostate Specific Antigen Working Group (PSAWG) criteria as follows:

1. Constant bone pain;
2. 50% increase in serial PSA level more than nadir in association with 2 ng/cc increase in PSA in patients who had 50% decrease in serial PSA level after initial therapy, which occurred despite suppressed level of testosterone (50 ng/dL);
3. 25% increase of nadir level in patients who did not have 50% decrease in serial PSA level after initial therapy, which occurred despite suppressed levels of testosterone (50 ng/dL);
4. Appearance of new lesions in bone scan or increased distant metastasis in imaging studies.

The inclusion criteria were age > 18 years, Eastern Cooperative Oncology Group performance status (PS) = 0 to 1, absolute neutrophil count $\geq 1500/mm^3$, platelet count at least 100 000/μL, bilirubin < 1 mg/dL, AST and ALT < 2.5 ULN, alkaline phosphatase < 2.5 ULN, serum creatinine < 1.5 mg/dL, or creatinine clearance at least 40 cc/mL. Patients should have no history of myocardial infarction within recent 6 months, no evidence of congestive heart failure or unstable angina, no history of previous chemotherapy for metastatic PCa, and no history of using thalidomide or taxotere. Patients with history of neuropathy, thrombophlebitis, brain metastasis, or other cancers within 2 years ago were excluded from the study.

A written informed consent was obtained from all the patients. The primary objective was to observe if there is any significant anti-tumoral activity of this regimen. Prostate-specific antigen response by 50% was determined as an acceptable cut off point and this finding must be approved by re-measurement of PSA level two weeks later.[7] Secondary objectives were time to progression of the disease, overall survival rate, and adverse effects.

Patients received taxotere (Aventis pharmaceuticals, Bridgewater, NJ) 75 $mg/m^2$ intravenously within 2 hours on the first day, which was repeated every 3 weeks. They also received thalidomide (Celgene Corporation; Warren, NJ) 50 mg/day and prednisolone 10 mg/day orally. Aspirin 80 mg/day was administered to all the patients as prophylaxis for thrombosis. Patients were treated with zometa or pegfilgrastim if necessary. In patients who did not undergo bilateral orchiectomy, medical castration with GnRH analogs was continued.

Patients were evaluated every 3 weeks before undergoing chemotherapy and their symptoms, signs, and PSA levels

were documented. All the patients had basal serum PSA level, bone scan, and computed tomography scan of the thorax, abdomen, and pelvic. These evaluations were repeated every 3 cycles. All responses were evaluated based on PSAWG criteria and response evaluation criteria in solid tumor (RECIST). The pain was evaluated by visual analogue scaling (VAS) from 0 to 10; as mild (0 to 2), moderate (3 to 5), severe (6 to 8), and very severe (9 to 10). Adverse effects were evaluated based on National Cancer Institute (NCI) common toxicity criteria version 3.0.[10,11]

The administration of taxotere was discontinued if grade IV hematologic toxicity or grade III non-hematologic toxicity was encountered. In grade III or IV neutropenia with taxotere administration, the drug was continued and pegfilgrastim was added 24 hours after taxotere administration. If patients developed grade IV febrile neutropenia after receiving pegfilgrastim, taxotere dose was reduced by 25%. If patients developed grade III or IV non-hematologic toxicity after receiving thalidomide or if grade II peripheral neuropathy was developed, thalidomide was discontinued. In patients that thalidomide was discontinued due to toxicity, treatment with taxotere and prednisolone was continued.

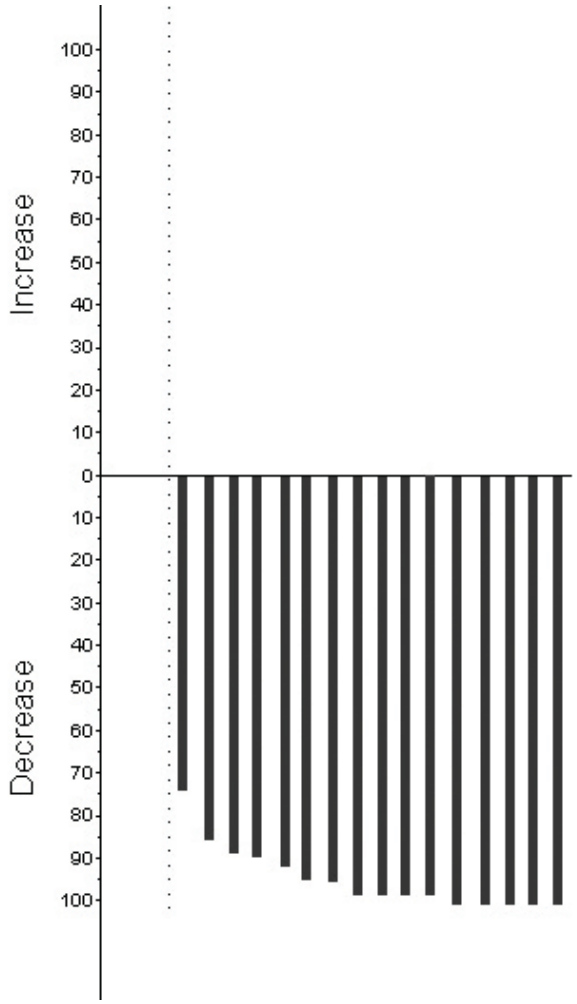


**Figure 1.** The percentage of difference in prostate-specific antigen level from baseline.

**Statistical Analysis**

The percentage of difference in PSA level from baseline to nadir level was calculated and reported as waterfall plot (Figure 1).[12] The number of patients who had ≥ 50% decrease in PSA level at any time, or ≥ 75% decrease in PSA level at any time, or ≥ 30% increase within the first 3 months of therapy was reported.

Complete response was defined as disappearance of all target or non-target lesions. Partial response was defined as at least 30% decrease in sum of maximal diameter of each lesion at baseline. Stable disease was defined as not sufficient shrinkage for partial response and not sufficient increase for progressive disease related to sum of maximal diameter of each lesion at baseline.

Considering secondary objectives, progression-free survival (PFS) was calculated at the recruitment time until appearance of the first evidence of disease progression or the last follow-up. Progressive disease was considered if each of the following items occurred:

1. 25% increase in the size of all soft tissue masses or presentation of new lesions. The partial response based on bone scan was considered when 2 or more new lesions disappeared, which were not matched with flare up of the disease;
2. Need to do radiotherapy;
3. Two times increase in PSA level more than 50% of nadir in patients who had PSA response and more than 25% increase from nadir or baseline PSA (either that was less), and also increase in absolute level of PSA at least 5 ng/mL that is confirmed by re-measurement for patients who were nonresponsive for PSA.

In patients that PSA level decreased, but did not reach the defined level at responsive criteria (PSA ≤ 50%), the progressive disease was defined as increase of PSA level to > 25% of nadir that should increase at least 5 ngr/cc.

The time of overall survival rate was determined from re-

cruitment time to death date (for any cause). Patients who remained in the study or were alive at the time of analysis were followed-up on the last day. The probability of PFS was estimated by Kaplan-Meier method (Figure 2).

## RESULTS

Mean age of the patients was 72.7 ± 5.39 years (range, 65 to 85 years). Mean Gleason score of the patients was 8 ± 0.71 (range, 6 to 8). The performance status was zero in 15 patients and 1 in one patient. Twelve patients had undergone prostatectomy and 4 had received radiotherapy. Fourteen patients only had bone metastasis and 3 only had soft tissue metastasis, while 2 patients had both soft tissue and bone metastases.

Mean serum level of PSA before treatment was 221.4 ± 165.3 ng/mL. Percentage of difference in PSA level from baseline to nadir was reported as waterfall plot. Ninety-four percent of patients had ≥ 50% decrease in PSA level and 87% (14 out of 16 patients) had ≥ 75% decrease in PSA level within the first 3 months of therapy.

Three patients had partial response in soft tissue. Sixteen (100%) adverse events were noted in 16 study subjects. Adverse effects were grade II fatigue in 10 (62%) patients, grade II weight loss in 3 (18%), peripheral neuropathy in 1 (6.2%), and grade I neutropenia in 2 (12%) patients. The PFS was 15 months and mean overall survival rate was 23 months.

## DISCUSSION

Taxotere is the first chemotherapeutic agent that improves survival rate in castration-resistant PCa. This finding was first reported in two independent phase III trials in 2004.[6,13] Following these trials, taxotere plus oral prednisolone were introduced as first-line standard therapy for hormone-resistant PCa.

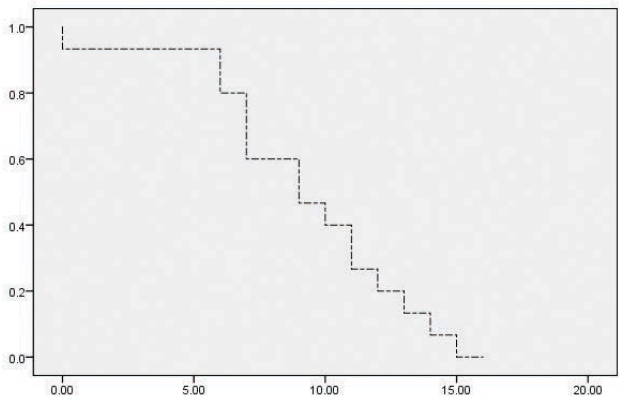


**Figure 2.** Kaplan-Meier plots of prostate-specific antigen non-progressive survival.

Prostate tumors should have angiogenic phenotype for progression to aggressive form.[14,15] Without angiogenesis, primary tumors of the prostate will remain indolent and their size will not exceed more than 3 mm. Thalidomide is an oral agent that inhibits angiogenesis, induces apoptosis in vitro, and reduces higher levels of angiogenic factors, such as VEGF and BFGF in patients with PCa.[9]

In a phase II trial that evaluated the efficacy of thalidomide on 63 patients with hormone-resistant PCa, PSA level reduced ≥ 40% in 27% of patients, and clinical symptoms disappeared in most of them.[16] In another phase II study on 75 patients with hormone-resistant PCa, patients were divided into two groups; first group received taxotere alone and second group received taxotere plus thalidomide. After 26.4-month follow-up, 53% of patients in second group had ≥ 50% decrease in PSA level compared to 37% decrease in the first group. Mean PFS in the first and second groups was 3.7 and 5.9 months, respectively ($P$ = .32). After 18 months, rate of overall survival was 42.9% in taxotere group and 68.2% in combination group.

In a randomized phase II trial on patients with hormone-resistant PCa, taxotere was used in combination with thalidomide or placebo in two groups of patients. Patients who received taxotere with thalidomide had higher rate of 50% PSA reduction (53% versus 37%) and also higher mean progression-free survival (5.9 versus 3.7 months; $P$ = .32). The overall survival rate in taxotere-thalidomide group was 29 months versus 15 months in other group.[7] The combination therapy was tolerated by most of the patients, but thromboembolic events occurred in 28% of patients who did not receive anticoagulant prophylaxis.

In our study, in 94% of patients who received the combination therapy, PSA decreased more than 50%. Mean time to progression was 15 months and mean survival rate was 23 months. The response rate of PSA and mean time to progression of disease were considerably raised. In a phase II clinical trial in which bevacizumab plus thalidomide, docetaxel, and prednisone were used in patients with hormone-resistant

PCa, high response rate of 50% reduction in PSA was 88% and PFS was 18.2 months.[17]

## CONCLUSION

Our study showed that addition of thalidomide to taxotere-prednisolone regimen was an effective combination therapy against hormone-resistant PCa with potential significant adverse effects.

## CONFLICT OF INTEREST

None declared.

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