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Phase 2 Trial of Monoamine Oxidase Inhibitor Phenelzine in Biochemical Recurrent Prostate Cancer

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Abstract

Purpose: Monoamine oxidase A (MAOA) influences prostate cancer growth and metastasis in pre-clinical models. We examined effects of phenelzine (a monoamine oxidase inhibitor) in patients with biochemical recurrent castrate-sensitive prostate cancer.

Materials and methods: An open-label single arm clinical trial enrolled subjects with biochemical recurrent prostate cancer defined by: PSA ≥ 0.4 ng/ml (post-prostatectomy) or PSA ≥ 2 ng/ml above nadir (post-radiation therapy); no evidence of metastasis on imaging; and normal

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Authors' contributions: MEG and JCS were responsible for trial conception and design. MEG, DBA, TD, JP, DQ were involved in study conduct including patient enrollment, treatment, and data collection. MEG, OC, PG assembled the data. MEG analyzed the data and drafted the report. All authors critically reviewed the manuscript and approved the final manuscript.

Declarations

Availability of data and material: The datasets used and/or analyzed during the current study are available from the corresponding author upon request.

Ethics approval and consent to participate: The clinical research protocol was approved by the Institutional Review Board (IRB) at the University of Southern California (USC), Los Angeles, California. All patients gave prospective consent to participate in all study procedures.

Consent for publication: Not applicable.

Conflict of interest: Dr. Gross serves as a consultant for Amgen and BeiGene and receives institutional research funding from Clovis Oncology, Glaxo-Smith-Kline, and BeiGene. Dr. Dorff serves as a consultant for Bayer, Noxopharm, Roche, and Seattle Genetics, is a speaker for Exelixis, and receives institutional research funding from Bayer. Dr. Quinn serves as a consultant for Astellas, AstraZeneca, Bayer, Genzyme-Sanofi, Jannsen, Clovis and Pfizer. Dr. Shih has a patent entitled ""Monoamine oxidase inhibitors and methods for treatment and diagnosis of prostate cancer. US Patent No. 9.771,625. The other authors declare no conflicts of interest.

androgen levels. Subjects received phenelzine 30 mg orally twice daily. Mood symptoms were assessed with the hospital anxiety depression score (HADS) questionnaire. The primary endpoint was the proportion of patients who achieved a PSA decline of ≥50% from baseline.

Results: Characteristics of the 20 eligible patients enrolled included: mean ± SD age 66.9± 4.8 years and PSA 4.7± 5.8 ng/dl. Maximal PSA declines ≥ 30% and ≥ 50% were observed in 25% (n=5/20) and 10% (n=2/20) of subjects, respectively. At 12 weeks, 17 subjects remained on treatment with PSA declines ≥ 30% and ≥ 50% of 24% (n=4/17) and 6% (n=1/17), respectively. Common toxicities observed included dizziness (grade 1 = 45%, grade 2= 35%), hypertension (grade ≥ 2 =30%), and edema (grade 1=25%, grade 2=10%). There was 1 episode of grade 4 hypertension (cycle 4) and 2 episodes of grade 3 syncope (cycle 12 and cycle 14) requiring treatment discontinuation. HADS questionnaires demonstrated a significant decrease in anxiety with no change in depressive symptoms on treatment.

Conclusions: Phenelzine demonstrated efficacy in patients with biochemical recurrent castrate sensitive prostate cancer. Most treatment related toxicities were mild, but rare significant and reversible cardiovascular toxicities were observed. Therapies directed at MAOA may represent a new avenue for treatment in patients with recurrent prostate cancer.

Trial registration: ClinicalTrials.gov Identifier: ClinicalTrial: NCT02217709

Keywords

prostate cancer; monoamine oxidase inhibitor; clinical trial

Introduction

Prostate cancer is the most common non-cutaneous cancer diagnosed in men in the United States with a projected annual incidence of ~174,650 cases diagnosed accounting for ~31,620 deaths in 2019(1). For most patients, prostate cancer is adequately treated with primary therapy which may include radical prostatectomy, radiation, or active surveillance. However, in about one third of patients, cancer recurs following primary therapy usually manifesting as an asymptomatic rise in plasma prostate specific antigen (PSA) level (2, 3). Biochemical recurrence (BCR) is defined by a confirmed elevation in PSA after primary therapy in the absence of clinically detectable metastatic disease (based on negative imaging studies) (4). Several trials have demonstrated clinical utility for salvage radiotherapy to the prostate bed in the post-prostatectomy setting (5). However, there is no general consensus for the treatment of BCR prostate cancer (6). While progression to overt metastatic cancer is a major concern, the median time from biochemical recurrence to the development of overt metastatic disease is between 8–10 years in most patients (7, 8). Androgen deprivation therapy will lower PSA in the vast majority of patients, but is associated with significant risks for adverse effects including osteoporosis, weight gain, decreased libido, fatigue, and potential exacerbation of cardiac disease leading many to question its use for early BCR prostate cancer (9). Overall, there is no consensus concerning the timing and use of ADT and other treatments for BCR prostate cancer (6).

Prior work led us to hypothesize that MAOA is an important therapeutic target in BCR prostate cancer which could be effectively targeted with a MAO inhibitor. Specifically,

MAOA is an androgen regulated gene (10) which is highly expressed in the basal cell layer of normal prostate glands (11) and in high grade prostate cancer(12). Genetic disruption of MAOA decreases development and growth of PTEN-driven prostate cancer in an animal model (13). MAO inhibitors decrease androgen receptor signaling and growth of androgen-responsive prostate cancer cell lines in vitro (14, 15)

MAO inhibitors were the first class of drugs used for the treatment of major depression in the 1950s (16). Concerns regarding side effects and the potential for rare and dangerous drug-drug and drug-food interactions led to decreased use as a treatment for major depression in the ensuing decades. However, as some patients with depression are refractory to newer anti-depressive agents, MAO inhibitors have continued to be used for select patients with major depression both in the US and worldwide (16, 17). Agents available in the United States include trancylpromine (Parnate), isocarboxacid (Marplan), selegiline (Deprenyl), and phenelzine (Nardil). Of these, phenelzine is a potent non-selective irreversible MAOA and MAOB inhibitor with an established safety record used for this study. Further, we have shown phenelzine to be active against prostate cancer cells in pre-clinical models (14). Thus, we sought to investigate if phenelzine would exert an anti-cancer effect demonstrated by decreasing PSA values in BCR prostate cancer patients.

Materials and Methods

Study Population

Subjects were required to have a history of histologically proven adenocarcinoma of the prostate with non-castrate levels of circulating testosterone and no evidence of metastatic cancer on imaging including a bone scan and CT scan of chest/abdomen/pelvis. Progressive disease was defined by any one of the following criteria: Post-radical prostatectomy: Any PSA ≥ 0.4 ng/ml or a confirmed rise ≥ 0.2 ng/ml (18); Post-primary radiotherapy: PSA ≥ 2 ng/ml above a post-radiotherapy nadir (19); Post-primary androgen-deprivation therapy: A confirmed rise of PSA ≥ 2 ng/ml above a post-therapy nadir. Patients were required to be ≥ 18 years of age with Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or less, and with adequate organ and hematologic function. Unfractionated testosterone levels were required to be in the non-castrate range (≥50 ng/dl). Major exclusion criteria included: history of major psychiatric disorder including schizophrenia, severe depression or mania requiring hospitalization; uncontrolled hypertension or recent cardiac events; use of medication contraindicated to be used along with phenelzine. The protocol was approved by the Institutional Review Board at the University of Southern California and registered with the US National Clinical Trials Registry (NCT02217709). Written informed consent was documented from all patients prior to the performance of any study related procedure.

Study Design and Methods

This single arm phase II clinical trial used the Simon's two-stage minimax design to explore efficacy of phenelzine for recurrent prostate cancer with the primary endpoint of detecting a PSA decline of ≥ 50% from the baseline value obtained at study entry (PSA50%)(20). The null hypothesis of a phenelzine PSA response ≤ 5% was compared to the alternate

hypothesis of ≥ 20% ($H_0 : P_0 \leq 0.05$ vs $H_1 : p_1 \geq 0.2$). In the first stage 12 subjects were required, the study was to be stopped if the response was observed in only one patient. As PSA 50% response was noted in 2 of the first 12 subjects, the study was expanded towards the goal of enrolling 21 subjects. However, due to funding limitations, the trial was stopped after 20 subjects were enrolled. A post hoc power analysis showed that by relaxing the power from 0.80 to 0.78 and maintaining the same significance level of 0.08, 20 subjects were sufficient to examine the original hypothesis.

The National Cancer Institute Common Terminology Criteria (version 4.0) was used to evaluate patient toxicity during each cycle. Adverse events were reported to authorities as required by institutional and regulatory guidelines. Every effort was made to administer the regimen at full dose, as tolerated. Standard supportive care measures were employed according to routine local practice. Subjects with a significant history of major psychiatric disorder (major depression, mania) were excluded and all subjects were screened for current psychopathology with the Hospital Anxiety and Depression Scale(21).

Patient self-reporting was used to monitor effect on mood symptoms using the Hospital Anxiety and Depression Scale (HADS) questionnaire which was administered at screening and prior to the start of every 3rd cycle thereafter. The HADS consists of a total of 14 items (HADS-T) used to assess anxiety (HADS-A, 7 items) or depression (HADS-D, 7 items) with scores ranging from 0–3 for each item (21). Subjects with score ≥11 on depression or anxiety HADS subdomains were discussed with the principal investigator before beginning or continuing on treatment.

Drug Treatment

Phenelzine was given orally starting on Cycle 1 Day 1 with each cycle consisting of 28 days. A dose escalation schedule was employed during the first two weeks of treatment to reach a target dose of 30 mg twice daily (total 60 mg per day) summarized as: (1) 15 mg once daily x 4 days; (2) 15 mg twice daily x 4 days; (3) 30 mg morning/15 mg evening; (4) 30 mg twice daily. After safety and tolerance was demonstrated in the first 10 subjects, the protocol was revised to include an additional dose level (45 mg twice daily) for patients treated at the target dose for ≥ 3 cycles without any grade ≥ 2 adverse events based on the FDA approved dose used for depression (22). Phenelzine was held for any drug-related toxicity considered ≥ grade 3 or any grade 2 toxicity considered particularly bothersome to the subject at the discretion of the treating physician. For any study related toxicities requiring treatment interruption, phenelzine was restarted according to the same dose escalation schedule as cycle 1 towards a target dose one level below the prior dose at which toxicity occurred. Reasons for treatment discontinuation included: treatment interruption for > 2 weeks for study-related toxicity, clinical progression, patient preference, or discretion of the treating physician. In all cases of treatment discontinuation, a taper schedule, decreasing phenelzine doses in increments of 15 mg every 4 days, was employed when possible. PSA levels were assessed at baseline and on day 1 of every 28 +/−5 day cycle.

Patients were educated about potential for drug:drug and drug:food interactions with verbal and written instructions provided at each visit. Patient education materials included cards

which specified avoidance of specific medications and limiting consumption of high-tyramine foods during phenelzine treatment (Supplementary Information).

Results

Patient Characteristics

Between November 2014 and July 2017, 20 evaluable patients were enrolled and received active treatment on the study. Baseline patient characteristics are summarized in Table 1 and included in detail in the Supplementary Table. Baseline assessments included: age (average ± SD) 66.9 ± 4.8 years, PSA 4.68 ± 5.80 ng/dl, PSA doubling time (PSADT) 18.1 ±−33.0 months, Testosterone,total 472 ± 209 ng/dl. Primary treatment included radical prostatectomy in 18 patients and radiation therapy in 2 patients. 8 subjects received radiotherapy as adjuvant or salvage treatment after radical prostatectomy and 1 subject underwent a salvage prostatectomy after radiation. Pathologic tumor staging is summarized as: pT2N0 (n=10), pT3N0 (n=7), pT3N1 (n=1). Cancer Gleason grade at diagnosis was available for all subjects summarized as: 3+3 (n=1), 3+4 (n=5), 4+3 (n=8), and ≥=8 (n=6). Average time from initial diagnosis to study treatment was 85 ± 53.6 months. Prior treatment history included a short course of androgen deprivation therapy (lasting ≤ 6 months) in 5 subjects concluding a median of 8 (2.7–14) years prior to study enrollment. Androgen recovery was required for all patients at enrollment.

Study Treatment Delivered

A total of 244 cycles of phenelzine were administered to 20 patients. The target dose of 60 mg per day was reached in 18 patients, 5 of which were escalated to 90 mg/day. The median number of treatment cycles delivered per patient was 12 (range 2–33). Three patients withdrew from the study after cycle 1 due to patient decision related to toxicity (n=2) or PSA elevation (n=1). Seventeen patients remained on study for 4 or more cycles and eight patients remained on study after 12 cycles. One patient completed study treatment after 19 cycles with stable disease when trial was stopped due to funding limitations. One patient was diagnosed with biopsy-proven lung metastasis after 33 cycles of treatment (10 years after original diagnosis of prostate cancer). Reasons for withdrawal for remaining patients were patient or physician discretion for increased PSA (n=9), toxicity (n=6), and patient withdrew consent/other (n=1).

PSA Modulation (Clinical Response)

Clinical response is summarized in Figure 1 and Table 2. PSA response was assessable in 20 subjects. Maximal PSA decline ≥ 50%, confirmed ≥ 4 weeks later, was achieved in 2 (10%) patients. Maximal PSA decline ≥ 30% was achieved in 5 (25%) patients. At the 12-week landmark time point, PSA decline ≥ 30% and ≥ 50% were noted in 4 (20%) patients and 1 (5%) patient, respectively. Overall, PSA declines were noted in 11 (55%) of during treatment on phenelzine with maximal PSA decline of 74% (range 5–74%). PSA values remained unchanged in 1 patient and exhibited progressive increases 8 patients over baseline values. Longitudinal follow-up for both patients exhibiting ≥ 50% PSA decline from baseline is provided in Figure 2.

Safety

Common treatment-related toxicities, expressed on a per patient basis, are summarized in Table 3. Neurocognitive adverse events were frequently observed most commonly reported as Grade 1 or 2 “dizziness” in ~80% of subjects. Fortunately, this was managed with dose-adjustment in many patients, but did contribute to early termination prior to 12 weeks for 2 subjects. Patients enrolled in the trial were carefully educated regarding drug:drug and drug:diet interactions specific to the MAOI drug class. However, there was 1 instance of grade 4 hypertension and 2 instances of grade 3 syncope requiring subject withdrawal (all without obvious dietary indiscretion and after >3 months on therapy) without any obvious history of dietary indiscretion by patient report. Most other toxicities were mild (grade ≤2), transient, and managed with dose adjustments as necessary. The median duration of treatment was 326 days (range 40–954 days).

Total testosterone levels were monitored in plasma at baseline and during study directed treatment. No significant change in testosterone levels were detected across study time points. Average total testosterone levels observed are summarized as: baseline 463± 237 ng/dl (n=20); cycle 2 467± 246 ng/dl (n=17); and cycle 4 484± 291 ng/dl (n=14). No correlation was observed between intra-patient variation in testosterone level and PSA modulation while on study.

Patient Reported Psychological Outcomes

Effect of study participation on mood symptoms were assessed by self-report using the HADS questionnaire administered at baseline and after every third cycle (Figure 3). Generally, HADS-T >14, HADS-A>7, or HADS-D >7 are used as a threshold values for screening cancer patients for additional psychiatric evaluation (23). The average HADS-A and HADS-D at baseline were 5.6 +/−3.6 and 1.9 +/− 2.4, respectively. HADS-A and HADS-D greater than 7 at baseline was observed in 7 and 1 subjects, respectively. After 3 cycles of therapy, we observed a significant decrease in mean HADS-A to 2.5 +/− 2.2 with no change noted in HADS-D (mean 1.9+/−2.2) in subjects who completed the questionnaire and remained on treatment (n=15, Student’s t-test, p=0.006).

Discussion

In this phase 2 trial involving patients with non-metastatic, castration-sensitive prostate cancer, treatment with phenelzine resulted in a ≥ 50% PSA decline in 10% of subjects. Eleven of 20 patients (55%) had measurable PSA decline compared to baseline with the greatest decline being 74%. Overall, we found phenelzine to be safe and well tolerated in this asymptomatic patient population with most patients (95%) reaching the target dose of 60 mg/ day for an average duration of treatment of 350 days (±263 days). The most common treatment related adverse events reflected the known MAOI related central nervous system effects including dizziness, fatigue, and somnolence. In general, these remained mild (grade 1) and were managed with dose adjustments. However, in two patients, grade 1 treatment related toxicity of dizziness led to subject withdrawal before completing 2 cycles.

A particular concern associated with the use of irreversible and MAOA/MAOB non-selective MAOIs such as phenelzine is the occurrence of transient hypertension associated with high dietary tyramine intake (termed the “cheese effect”) (24). Perhaps not as well-known is transient hypotension which may also be associated with these agents (25). In this trial, regular evaluation for cardiovascular signs and symptoms (generally every 4–6 weeks) and patient education cards were used to minimize cardiovascular risks and avoid exposure to high-tyramine foods. However, we did observe cardiovascular adverse events on trial which included grade 4 hypertension (1 subject) and grade 3 syncope (2 subjects) requiring subject withdrawal. All of these significant cardiovascular adverse events occurred without obvious dietary indiscretion and after more than 3 months of therapy. As these events were both rare and reversible and the median duration of treatment on the trial approached one year (326, range 40–954, days), we conclude that phenelzine is safe to administer to prostate cancer patients without pre-existing psychiatric or neurologic diseases when used with close monitoring in this setting with emphasis that educating patients about dietary restrictions is key to safety.

As MAOIs are best known as anti-depressants with a recommended therapeutic dose range of 60–90 mg daily, we used the HADS questionnaire to explore mood effects associated with phenelzine treatment in patients in the absence of an overt psychiatric disorder. At baseline, potentially clinically significant anxiety (HADS-A>7) was observed in 7 of 20 subjects (35%). Anxiety relating to PSA laboratory values has been associated with screening and treatment decision making in prostate cancer (26, 27). Interestingly, we observed a significant decrease in the HADS-A index following 3 months of treatment with phenelzine. In this open-label trial, it is impossible to determine if the decrease in anxiety was a direct pharmacologic effect of MAOI treatment or a non-specific placebo effect related to clinical trial participation. Regardless, the data does suggest that anxiety is prevalent in patients with biochemically recurrent prostate cancer and additional studies may be needed to address more fully this as an important quality of life issue in prostate cancer patients following primary therapy.

The main limitations of this study include lack of a placebo control group and the small sample size. Biochemical recurrent prostate cancer is notoriously heterogeneous in clinical course with a very long natural history that can extend for many years from the time PSA elevation to the development of overt metastatic disease. It is possible that the short-term effects observed on PSA levels may not translate to significant delays in clinically significant endpoints such as metastatic progression or overall survival. In general, an appropriately powered randomized clinical trial would be required to demonstrate effects on time to progression endpoints.

To our knowledge, this study represents the first clinical trial to demonstrate activity of a MAOI in human cancer. Additional studies are planned to identify biomarkers of clinical benefit and to explore how MAOI based therapy may be best applied to the treatment of men with prostate cancer.

Conclusions

In summary, we found phenelzine to be relatively well tolerated in men with biochemical-recurrent, non-metastatic castrate sensitive prostate cancer and lowers PSA in 25% of men. Further studies would be needed to determine if MAOIs, used alone or in combination with other agents, may delay clinical progression and metastasis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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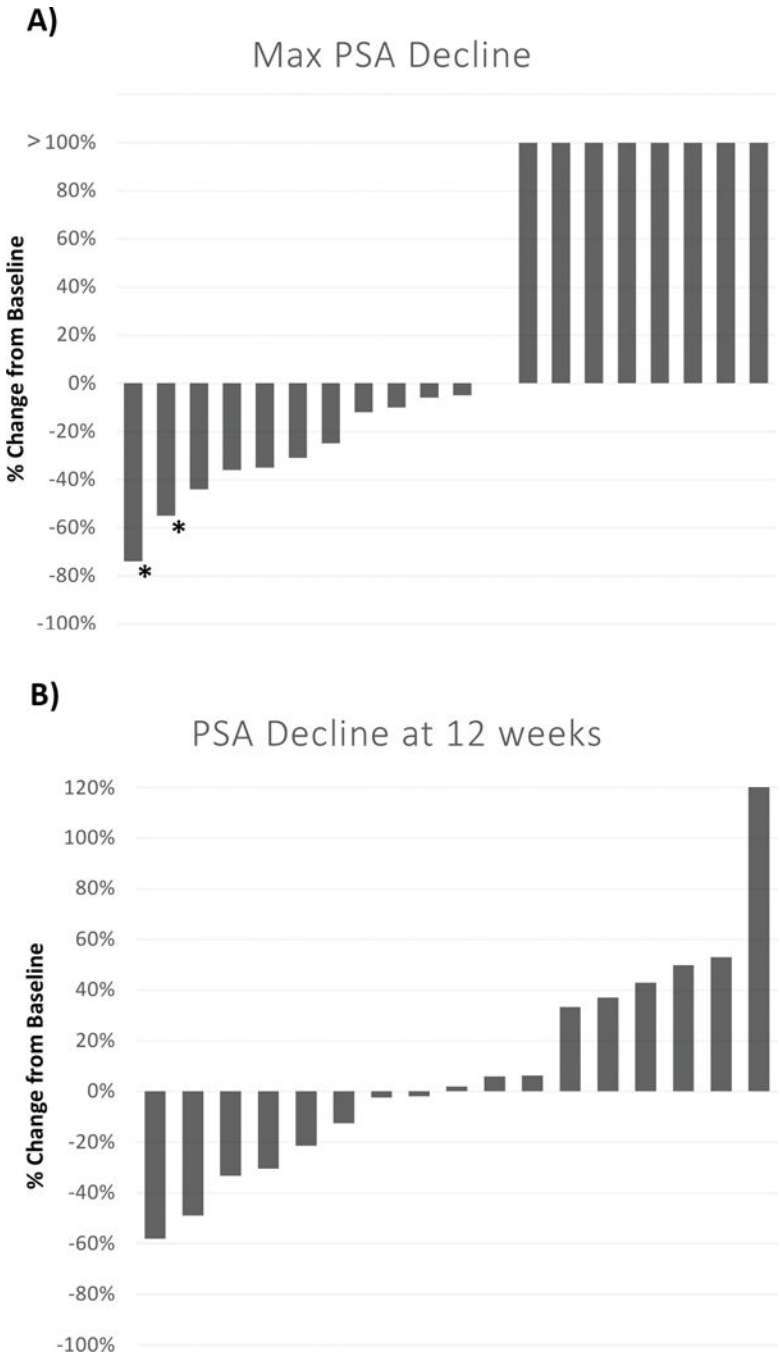

Figure 1. Changes in PSA relative to phenelzine treatment.

Maximal percent PSA change per patent on treatment. Maximal (a) and change at 12 weeks (b) from baseline. *: denotes PSA decline ≥ 50% confirmed > 4 weeks.

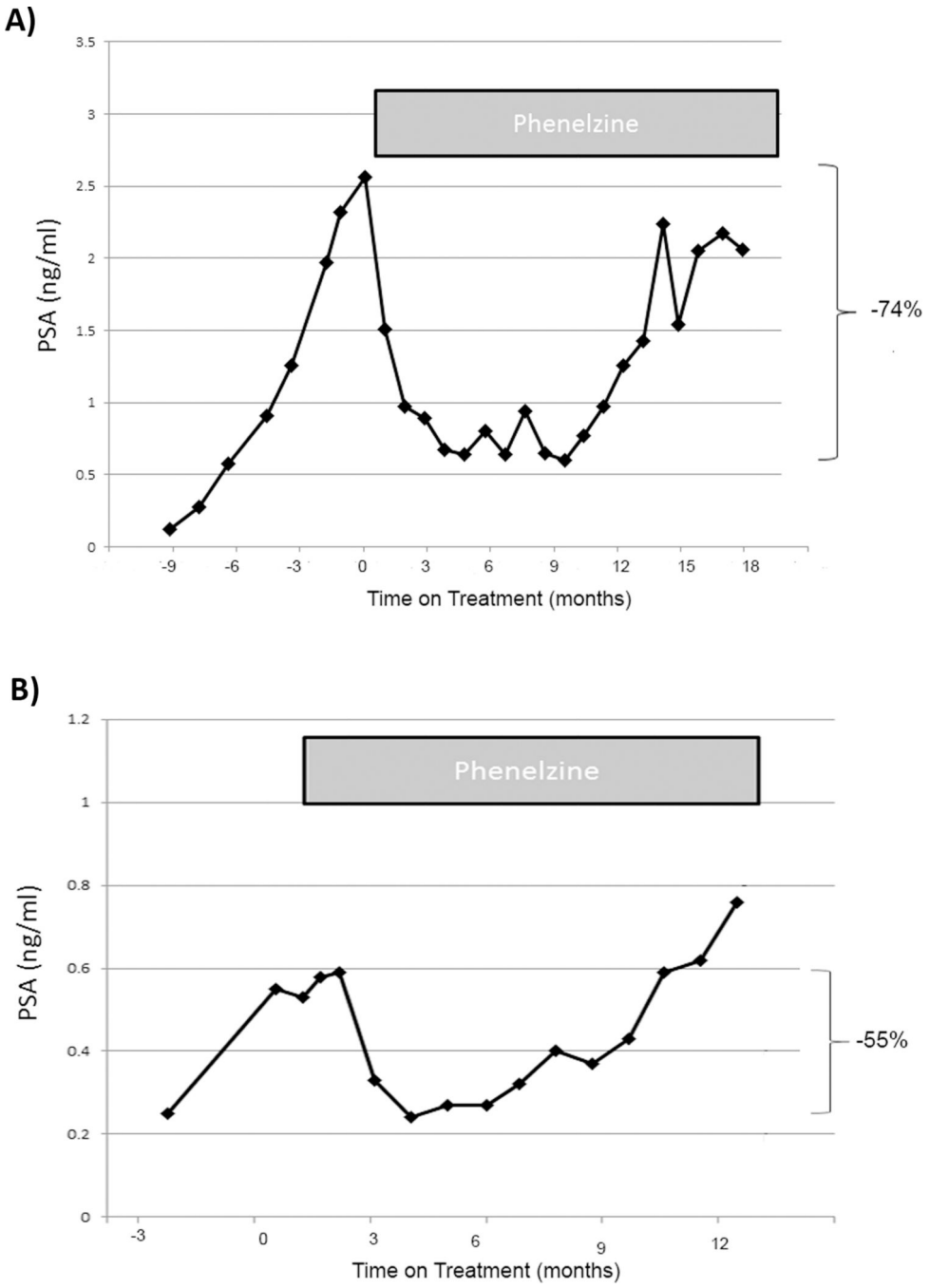

Figure 2.

Longitudinal analysis of PSA levels over time in subject 4 (A) and subject 14 (B) with ≥ 50% PSA Decline.

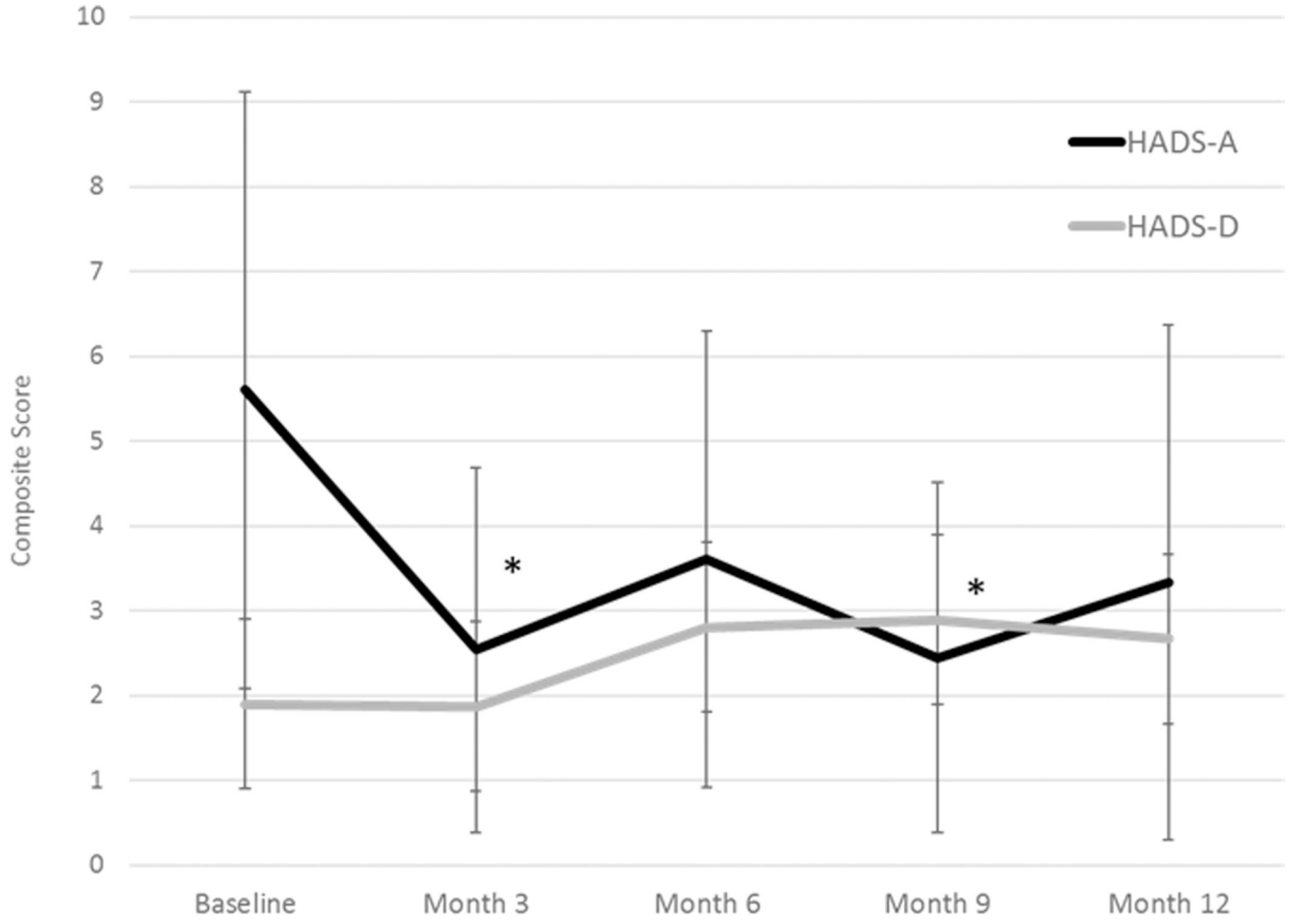

Figure 3:

Changes in patient self-report of mood symptoms on treatment. Hospital Anxiety and Depression Scale scores for anxiety and depression were tabulated at baseline, and every 3 months at specified time points. *: $p<0.05$, Student's t-test compared to baseline.

Table 1.

Demographic and Baseline Characteristics of 20 Evaluable Patients

	Median (range)	**Mean (SD)**
Age (Years)	67.2 (58–73)	66.9 (4.8)
PSA (ng/ml)	2.27 (0.36–24.62)	4.7 (5.8)
Testosterone, total (ng/dl)	431 (174–1136)	472 (209)
Time from diagnosis to study entry (months)	73 (21–190)	85 (53.6)
Race		
White	18 (90%)	
African-American	1 (5%)	
Native American	1 (5%)	
Ethnicity		
Non-Hispanic or Latino	20 (100%)	
Hispanic/Latino	0 (0%)	
Prior Treatment	**Number (%)**	
Prostatectomy Alone	10 (50%)	
Radiation Alone	1 (5%)	
Prostatectomy and radiation	9 (45%)	
Gleason grade at diagnosis		
3+3=6	1	
3+4=7	5	
4+3=7	8	
≥ 8	6	

Table 2.

PSA Change from Baseline

Maximum Decline (n=20)	
≥ 30%	5 (25%)
≥ 50%	2 (10%)
Decline at 12 weeks (n=17)	
≥ 30%	4 (24%)
≥ 50%	1 (6%)

Table 3.

Treatment Related Toxicity

		NCI Toxicity Grade			
Body System	**CTC Name**	**1**	**2**	**3**	**4**
Eye Disorders	Blurred Vision	2	0	0	0
Gastrointestinal Disorders	Constipation	3	0	1	0
	Diarrhea	1	0	1	0
	Dry mouth	7	0	0	0
	Nausea	2	0	0	0
	Stomach pain	1	0	0	0
General Disorders and Administration Site Conditions	Edema limbs	5	2	0	0
	Fatigue	7	1	0	0
Investigations	Alanine aminotransferase increased	2	0	0	0
	Aspartate aminotransferase increased	2	0	0	0
	Weight gain	1	3	1	0
Nervous System Disorders	Dizziness	9	7	0	0
	Headache	3	0	0	0
	Memory impairment	1	0	0	0
	Movements involuntary	3	0	0	0
	Somnolence	6	0	0	0
	Syncope	0	0	2	0
	Tremor	2	0	0	0
Psychiatric Disorders	Agitation	1	0	0	0
	Anorgasmia	2	0	0	0
	Anxiety	1	0	0	0
	Confusion	6	0	0	0
	Depression	1	0	0	0
	Insomnia	2	0	0	0
Vascular Disorders	Hypertension	0	4	1	1
	Hypotension	1	1	1	0