A Phase II trial of a combination herbal supplement for men with biochemically recurrent prostate cancer

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BACKGROUND: Men with biochemical recurrence (BCR) of prostate cancer are typically observed or treated with androgen-deprivation therapy. Non-hormonal, non-toxic treatments to slow the rise of PSA are desirable. We studied a combination herbal supplement, Prostate Health Cocktail (PHC), in prostate cancer cell lines and in a population of men with BCR.

METHODS: PC3, LAPC3 and LNCaP cells were incubated with increasing concentrations of PHC suspension. Men previously treated for prostate cancer with surgery, radiation or both with rising PSA but no radiographic metastases were treated with three capsules of PHC daily; the primary end point was 50% PSA decline. Circulating tumor cells (CTCs) were identified using parylene membrane filters.

RESULTS: PHC showed a strong dose-dependent anti-proliferative effect in androgen-sensitive and independent cell lines in vitro and suppression of androgen receptor expression. Forty eligible patients were enrolled in the clinical trial. Median baseline PSA was 2.8 ng ml⁻¹ (1.1–84.1) and 15 men (38%) had a PSA decline on study (1–55% reduction); 25 (62%) had rising PSA on study. The median duration of PSA stability was 6.4 months. Two patients had grade 2/3 transaminitis; the only other grade 2 toxicities were hyperglycemia, hypercalcemia and flatulence. There were no significant changes in testosterone or dihydrotestosterone. CTCs were identified in 19 men (47%).

CONCLUSIONS: Although the primary end point was not met, PHC was well tolerated and was associated with PSA declines and stabilization in a significant number of patients. We believe this is the first report of detecting CTCs in men with BCR prostate cancer. Randomized studies are needed to better define the effect of PHC in men with BCR.

INTRODUCTION

Although most men who develop a rising PSA after curative therapy will not die from prostate cancer, these men with biochemical recurrence (BCR) face uncertainty about when they will develop metastases and when they should start on androgen-deprivation therapy (ADT). To date, no study has shown a survival advantage for initiation of ADT at BCR rather than at the time radiographic metastases are detected. Furthermore, there is an increasing evidence of significant harms caused by ADT, including weight gain, loss of lean muscle, development of diabetes and osteopenia.¹,² Thus, aside from salvage radiation, there is no standard of care, but options include observation or intermittent ADT.³ However, anxiety is an important driver of patients receiving ADT for BCR⁴ despite known decrements to quality of life related to treatment.³ Non-hormonal, non-toxic treatments that could lower or slow the rise of PSA are highly desirable. Multiple natural remedies have been studied in this setting, such as pomegranate juice⁵ and fenretinide.⁶ In the fenretinide study, zero of 23 men experienced a PSA decline, which indicates that observation or treatment with an inactive agent would be expected to result in continued PSA rise for all the patients.

Prostate Health Cocktail (PHC) was formulated to include ingredients that had shown varied mechanisms of action influencing prostate cancer growth in preclinical studies in the following concentrations: vitamin D3 (cholecalciferol) 400 IU, vitamin E (alpha tocopherol) 400 IU, selenium (L-selenomethionine) 200 mcg, green tea extract (epigallocatechin) 400 mg, saw palmetto berry (perminox) 320 mg, soy isolavones (genistein and daidzein) 20 mg each, and lycopene 10 mg. For instance, vitamin D receptors are present on prostate cancer cell lines PC3, LNCaP and DU145⁷ and treatment with vitamin D3 in culture resulted in decreased proliferation and increased differentiation.⁸,⁹ In men with BCR, daily use of oral calcitriol, a high potency vitamin D analog, was associated with >50% PSA reductions, but this benefit was offset by clinically significant hypercalcemia.¹⁰ Vitamin E has also been identified as a nutrient of interest, as the Finnish ATBC study found an incidental reduction in prostate cancer mortality in men taking vitamin E (α-tocopherol) compared with placebo.¹¹ One potential mechanism of action is inhibition of androgen receptor (AR) signaling as a transcriptional repressor, with resultant reduction in expression of PSA.¹² Additional studies have confirmed that vitamin E, and lycopene as well, can induce tumor necrosis in xenograft models, while downregulating androgen target genes, such as interleukin-6, and insulin growth factor 1.¹³ Selenium was also unexpectedly found to be associated with a lower risk of prostate cancer in an unrelated prevention study,¹⁴ though subsequent prospective study failed to confirm this effect.¹⁵ In established cancer, selenium has been shown to...

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exert a multitude of effects on cells, inducing cell cycle block and apoptosis via superoxide and caspase-9, as well as downregulating the angiogenic switch \(^1\) and works synergistically with vitamin E to inhibit cancer cell growth. \(^1\) Green tea polyphenols such as epigallocatechin diminish AR signaling and lower circulating hepatocyte and vascular endothelial growth factor. \(^1,2,9\) Saw palmetto inhibits growth of LNCaP cells with decreased expression of cyclooxygenase 2. \(^2,1\) Soy isoflavones genistein and daidzein concentrate in prostate tissue, \(^2,9\) where they interfere with DNA synthesis and methylation, increase expression of cell cycle regulators and decrease VEGF expression. \(^21\) Synergism has also been identified between lycopene and vitamin D3, with an additive effect on cell differentiation and inhibition of proliferation. \(^28\)

We undertook preclinical and clinical study of PHC with the hypothesis that combination herbal therapy would be effective in lowering PSA in men with BCR of prostate cancer. Because better stratification tools are needed for BCR, we also studied the detection of circulating tumor cells (CTCs) in this population. Although traditional methods have failed to reliably detect CTCs in BCR prostate cancer patients, we incorporated the use of a novel parylene membrane filter technology to see whether a non-EpCAM enrichment-based technique would identify CTCs in this population.

### MATERIALS AND METHODS

In addition to obtaining an IND from the FDA (no.79 284), the content of PHC was independently confirmed by NHK Laboratories, Inc. (Santa Fe Springs, CA, USA) (COA issued 8/2/2012).

Cell culture and proliferation assay

Human prostate cancer LNCaP, PC3 and LAPC3 cells (American Type Culture Collection, Manassas, VA, USA) were cultured and maintained at 37 °C in a 5% CO2 atmosphere in RPMI-1640 medium supplemented with 10% fetal bovine serum, 100 units ml\(^{-1}\) penicillin and 100 μg ml\(^{-1}\) streptomycin. Prostate cancer cells were seeded into 96-well plates (3000 cells per well) to grow to 80% confluency prior to treatment.

The dry PHC powder was dissolved in serum-free RPMI 1640 (SF-RPMI, 100 mg ml\(^{-1}\)) by shaking for 2 h at room temperature. After spinning (13,000 r.p.m.), the supernatant was filtered (0.2 μm), then diluted with SF-RPMI and added to the cell culture. The cells were treated with PHC at final concentrations of 0 (SF-RPMI as the vehicle control), 0.01, 0.1 and 1 mg ml\(^{-1}\). Following 72 h of incubation at 37 °C in a 5% CO2 atmosphere, the cells were washed and subjected to the MTS assay (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium) assay. The CellTiter 96 AQsulfu One Solution Cell Proliferation Assay kit (Promega, Madison, WI, USA) was used following the manufacturer's instructions. The absorbance was detected at 490 nm with a Microplate Reader (VersaMax, Molecular Devices, Sunnyvale, CA, USA). All analyses were performed in a quadruplicate set of wells and repeated on separate occasions. AR expression was examined by western blotting. The PHC-induced apoptosis was examined by identifying DNA fragmentation with fluorescent TUNEL (terminal deoxynucleotidyl transferase-mediated dUTP-fluorescein nick end labeling) assay and counter-staining with DAPI (4,6-diamidino-2-phenylindole). All apoptotic (TUNEL-positive) cell nuclei had bright green appearance under a fluorescence microscope (Olympus, Tokyo, Japan).

Clinical trial

The protocol was IRB approved and registered on clinicaltrials.gov website (NCT00669656). Men were eligible for the trial if they had BCR after treatment for prostate cancer with curative intent using prostatectomy, radiation therapy or both. At least two rising PSA values ≥2 weeks apart were required, with a minimum absolute PSA of 1 ng ml\(^{-1}\) for prostatectomy patients and 2 ng ml\(^{-1}\) for radiation patients; radiation patients had to meet the ‘nadir plus two’ definition of recurrence. PSA doubling time (DT) had to fall between 3 and 36 months. There had to be no radiographic evidence of metastases on a bone scan ≤12 weeks and a CT scan ≤8 weeks prior to enrollment. Men who had received ADT were eligible, provided the following criteria were met: for neoadjuvant and adjuvant ADT, a total of 24 months were allowed provided the last injection was ≥12 months prior to enrollment. For men treated with ADT for BCR, they could not have demonstrated castration resistance (≥2 rising PSA values with testosterone <50), they had to be off ADT for at least 3 months with testosterone recovery >150 ng dl\(^{-1}\) and there had to be a documented discussion with the treating physician about the decision not to use ADT again. Normal organ function was required: calculated creatinine clearance ≥ 50 ml min\(^{-1}\); aspartate aminotransferase, alanine transaminase and bilirubin all had to be ≤ 1.5 × upper limit of normal. Men taking full-dose anticoagulation or antiplatelet therapy were excluded; however, the use of 81 mg aspirin daily was allowed. Significant cardiac disease, including coronary disease with prior bypass surgery or stent placement, resulted in exclusion. Subjects were provided with PHC by OncoNatural Solutions (Los Angeles, CA, USA) and were instructed to consume three capsules daily on an empty stomach; 4 weeks constituted a treatment cycle. Toxicity assessment (Common Terminology Criteria for Adverse Events, CTC AE v 3.0) and PSA testing occurred after one cycle and then every 2 cycles for up to 1 year. Imaging was to be done as clinically indicated, with a recommended reassessment at the time of removal from study. Subjects

![Figure 1. Prostate Health Cocktail (PHC) suppresses the proliferation of prostate cancer cell lines dose-dependently and suppresses androgen receptor (AR) expression. Human prostate cancer LNCaP, PC3 and LAPC3 cells were seeded into 96-well plates (3000 cells per well) to grow to 80% confluency prior to treatment. The dry PHC powder was dissolved in serum-free RPMI 1640 (SF-RPMI) and added to the cells at the final concentrations of 0 (SF-RPMI as the vehicle control), 0.01, 0.1 and 1 mg ml\(^{-1}\), respectively. Following 72 h incubation at 37 °C in a 5% CO2 atmosphere, the cells were washed and subjected to the MTS assay. The result was expressed as an apoptotic index determined as the mean of TUNEL-positive cells counted per × 400 field.](image)
were removed from study for PSA progression, which had to be confirmed by a second PSA value 4 weeks after initially meeting criteria and in the absence of documented urinary tract infection or prostatitis. For patients whose PSA levels never decreased on study, PSA progression was defined as a 25% increase over baseline and an absolute increase of 5 ng ml\(^{-1}\). In patients whose PSA initially decreased on study, PSA progression was defined as a 25% increase and an absolute increase of 5 ng ml\(^{-1}\) above nadir or crossing above the baseline PSA level. Subjects who were still felt to be benefiting from treatment after completing all protocol-specified treatment (13 cycles) were eligible to continue receiving PHC at no cost from the manufacturer off protocol, while being followed by their regular physician. The trial was funded by the Whittier Foundation.

The primary end point was PSA response, initially defined as a 50% reduction in PSA. Subjects whose PSA did not meet progression criteria (as defined above) by 12 weeks or response were labeled as PSA stable disease for their best response. PSA DT posttreatment was calculated using all available values > 1 month after starting study therapy; only subjects with repeat PSA measurements available after starting study therapy were evaluable.

The study was originally designed with the assumption that, left untreated, > 95% of men meeting inclusion criteria would continue to have rising PSA and that a 15% rate of PSA declines would represent activity worthy of additional study. A Simon Optimum two-stage design was employed,\(^{30}\) with interim analysis after 20 subjects. With no responders, study closure would be considered. If enrollment continued, response in ≥ 4 of the 45 subjects would indicate sufficient PHC activity to warrant further study. With this design, there was 0.9 probability (power) to conclude that PHC was worth of further study when the true response rate was ⩾ 15%, and 0.1 probability (alpha) of incorrectly considering PHC worthy of further study with a true response rate < 4%. At the time of the interim analysis with 20

\[\text{Figure 2.} \] Prostate Health Cocktail (PHC) induces apoptosis in prostate cancer cells. Three cells lines, LNCaP, LAPC3 and 22RV1, of prostate cancer were cultured on cover slips and treated with PHC (10 µg ml\(^{-1}\)) for 4 days. The PHC-induced apoptosis was examined by identifying DNA fragmentation with fluorescent TUNEL (terminal deoxinucleotidyl transferase-mediated dUTP-fluorescein nick end labeling) assay and counter-staining with DAPI (4,6-diamidino-2-phenylindole). All apoptotic (TUNEL-positive) cell nuclei had bright green fluorescence under a fluorescence microscope. The result was expressed as an apoptotic index defined as the mean of TUNEL-positive cells counted per × 400 field. * \(p<0.05\) indicated significant difference. Representative photomicrographs demonstrated the DNA fragmentation and dysmorphic nuclear condensation (Figure 2a), which were significantly increased in response to PHC treatment in all three cell lines (Figure 2a, D–F, J–L, P–R, Figure 2b).

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Table 1. Baseline and demographic characteristics of the study population

| Number of patients | % |
|--------------------|---|
| Age at the study entry (years), median (range) | 67 (54.8–84.5) |
| Race               |   |
| Caucasian          | 28 | 70 |
| Hispanic           | 6  | 15 |
| Black              | 4  | 10 |
| Asian              | 2  | 5  |
| Gleason score at initial diagnosis |   |
| ≤ 7                | 31 | 78 |
| > 7                | 9  | 23 |
| Prior treatment    |   |
| Radiation therapy only | 10 | 25 |
| Surgery only       | 10 | 25 |
| Surgery + radiation therapy | 20 | 50 |
| Neo-adjuvant/adjuvant ADT | 9  | 22.5 |
| ADT for biochemical recurrence prior to study entry | 3  | 7.5 |

Abbreviation: ADT, androgen-deprivation therapy.

RESULTS

Experiments using LAPC3, PC3 and LNCaP cell cultures identified a strong dose-dependent anti-proliferative effect (Figure 1) as well as suppression of AR expression by western blotting in LNCaP and LAPC3 cells. AR was not detectable in PC3 cells (data not shown). Apoptosis was induced by exposure to PHC, as detected by the TUNEL assay (Figure 2), in all three cell lines.

Of the 43 subjects enrolled, 3 were found to be ineligible due to low baseline testosterone (1), use of excluded medication (1) or history of coronary artery disease (1). Baseline and demographic characteristics of the 40 eligible subjects are summarized in Table 1. The median age was 67 years (range 54–84) and baseline PSA was 2.8 ng ml⁻¹ (1.1–84.1). For initial local therapy, 10 men (25%) were treated with radiation, 10 men (25%) had prostatectomy only and 20 men (50%) had received both. Of these 40, 12 men (30%) had received ADT prior to study entry; 3 for BCR and 9 as (neo)adjuvant. The median baseline PSA DT was 9.4 months (range 3.3–36.1) and was slower in those with Gleason ≤ 7 (12 months) compared with Gleason 8–10 (7.2 months), P = 0.031.

Subjects received a median of 10 cycles (1–13) of treatment; 26 subjects (65%) received treatment for at least 6 months and 8 (20%) were still on treatment at 12 months. Reasons for discontinuation included PSA or clinical progression in 19 (48%) and completion of protocol therapy in 11 (28%), initiating alternative treatment for rising PSA without meeting progression criteria in 6 (15%), difficulty complying with study procedures in 2 (5%), toxicity in 1 and intercurrent illness in 1. The patient who took off therapy early due to intercurrent illness did not have posttreatment PSA measurements; the other 39 subjects were evaluable for assessing PSA response. None of the 39 subjects experienced a complete PSA response or a confirmed PSA partial response (defined as a 50% decrease from baseline, which was confirmed at least 4 weeks later). However, one patient achieved a 55% decrease at cycle 13; he was taken off therapy due to completion of protocol. Fifteen of the 39 evaluable patients (38%) had a PSA decline with a maximum decrease ranging from −1.1% to −55%. Of the 38 men evaluable at 12 weeks, 9 (24%) had PSA decline (Figure 3). The median ‘best’ PSA change at any time point during the study for all the 39 evaluable subjects was 3.8% (range: −55% to +34.3%) and the median change in PSA at 12 weeks was 18.1% (range: −17.5 to +78.0%). The median time to PSA or clinical progression was 8.3 months (95% confidence interval (CI): 5.5, 11.8). The median duration of PSA stability (from treatment start date to last assessment, without PSA progression) was 6.4 months (range: 0.6–27.5). PSA DT posttreatment was calculated for 37 men who had 2+ posttreatment PSA determinations. Median PSA DT posttreatment was 6.7 months (20 7.7) compared with 9.4 months at study entry (P = 0.047, sign test); 12 of the 37 evaluable men (32%) had a slower PSA DT posttreatment than at baseline. The median follow-up is 17.8 months (range 0.9–35.6) and 18 men have had clinical progression, with local...
recurrence (n = 2) or distant metastatic disease (n = 16); all but one of these progressions occurred after the patient had been taken off the PHC supplement. The median time to metastasis from study treatment start was 23 months (95% CI 13.6, 33.8 months).

Toxicity data are summarized in Table 2; there were no grade 4 toxicities. The only grade 3 toxicity deemed possibly related to study therapy was transaminitis, which resolved upon stopping treatment. On review, this transamnitis seemed related to alcohol intake. However, as grade 1 and 2 transaminitis were noted in three other patients, the possibility that this toxicity was related to PHC cannot be ruled out. One patient developed grade 3 hyponatremia and altered mental status in the setting of pneumonia, which was felt to be unrelated to PHC. There were no consistent significant changes in selenium, testosterone or DHT during study therapy (Table 3) although selenium levels increased from baseline to latest cycle (P = 0.002) for the subset of 15 patients with data.

CTCs were collected in 33 patients at baseline and identified in 16 (48%); 22 of the 33 patients also had specimens collected at follow-up, and CTCs were identified in 10 (45%) of these 22 patients. Among patients with CTCs assessed at baseline and follow-up, the CTC count increased in 5 men and decreased in 7 men; the remaining 10 had no change. The presence of CTCs was not associated with baseline PSA DT (P = 0.58) or with PSA levels at 12 weeks posttreatment (P = 0.44) or the development of metastases (P = 0.30).

**DISCUSSION**

There is a substantial population of men with BCR after curative-intent local therapy for prostate cancer. Although 20% of these men will die from prostate cancer, the natural history is lengthy.

Our current risk stratification tools for prostate cancer mortality are clinical: PSA DT and Gleason score.  

Table 2. A summary of toxicities experienced by patients during the clinical trial

| Toxicity category | Toxicity | Number of patients with maximum grade experienced |
|-------------------|----------|--------------------------------------------------|
| Blood/bone marrow| Hemoglobin| 1 0 0 0 |
|                   | Leukocytes (total WBC)| 1 0 0 0 |
|                   | Platelets| 1 0 0 0 |
| Cardiac general   | Hypertension| 1 0 0 0 |
| Constitutional symptoms | Fatigue (asthenia, lethargy, malaise)| 2 0 0 0 |
| Dermatology/skin  | Rash/desquamation| 1 0 0 0 |
| Endocrine         | Glucose, serum-high (hyperglycemia)| 3 1 0 0 |
| Gastrointestinal  | Constipation| 2 0 0 0 |
|                   | Diarrhea| 1 0 0 0 |
|                   | Distension/bloating, abdominal| 2 0 0 0 |
|                   | Flatulence| 3 1 0 0 |
|                   | Heartburn/dyspepsia| 4 0 0 0 |
|                   | Nausea| 2 0 0 0 |
| Hemorrhage/bleeding| Hemorrhage/bleeding—Other| 1 0 0 0 |
| Hepatic           | ALT, SGPT| 1 1 1 0 |
|                   | AST, SGOT| 2 1 0 0 |
|                   | Alkaline phosphatase| 1 0 0 0 |
|                   | Bilirubin (hyperbilirubinemia)| 2 0 0 0 |
| Metabolic/laboratory | Calcium, serum-high (hypercalcemia)| 0 1 0 0 |
|                   | Creatinine| 1 0 0 0 |
|                   | Potassium, serum-high (hyperkalemia)| 2 0 0 0 |
| Musculoskeletal/soft tissue | Muscle weakness, generalized or specific area| 2 0 0 0 |
| Neurology         | Dizziness| 1 0 0 0 |
| Pain              | Pain (abdomen NOS)| 2 0 0 0 |
|                  | Pain (muscle)| 0 1 0 0 |

Abbreviation: ADT, androgen-deprivation therapy; ALT, alanine transaminase; AST, aspartate aminotransferase; NOS, nitric oxide synthase; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; WBC, white blood cell.

Table 3. Changes in hormone and micronutrient levels during the study

| Markers | Cycle 1 (baseline) | Cycle 4 or last cycle after cycle 1 | Cycle 13 or last cycle after cycle 4** | P-value* |
|---------|--------------------|-------------------------------------|--------------------------------------|--------|
| N       | Median (range)     | N Median (range)                   | N Median (range)                     | Cycle 4 vs baseline | Cycle 13 vs baseline | Cycle 13 vs cycle 4 |
| PAP (ng dl⁻¹) | 38 1.2 (0.4–10.7) | 30 1.1 (0.5–7.8) | 16 1.3 (0.4–8.0) | 0.25 | 0.58 | 0.79 |
| Testosterone (ng dl⁻¹) | 39 370 (35.6–736) | 30 355 (192–905) | 18 374 (214–624) | 0.26 | 0.24 | 1.00 |
| DHT (ng ml⁻¹) | 36 29.5 (9–74) | 28 27 (9–91) | 16 31 (15–61) | 0.31 | 1.00 | 0.79 |
| Vitamin D (ng ml⁻¹) | 40 33 (22–107) | 30 37 (12–63) | 15 36 (23–75) | 0.33 | 0.58 | 0.77 |
| Selenium (mcg l⁻¹) | 37 149 (88–298) | 27 151 (104–316) | 15 171 (134–414) | 0.56 | 0.002 | 0.58 |

Abbreviations: DHT, dihydrotestosterone; PAP, prostatic acid phosphatase. *P-value based on sign test. **n=15; 1 patient from cycle 9, 1 from cycle 10, 8 from cycle 12, 5 from cycle 13.
randomized trials have yet shown that ADT improves survival when administered at BCR compared with when metastases are detected. Aside from radiation +/- ADT for BCR, the NCCN guidelines for this group of patients includes observation although intermittent ADT has also been utilized. In this study, 15/39 (38.5%) of men experienced a PSA decline, and 9 of 36 (25%) had a decline at 12 weeks compared with baseline. Strengths of this study include rigorous testing of PHC for manufacturing and content. Nutritional supplements are not strictly regulated, which means that content may not be consistent, making sound clinical investigation difficult. Prior experience with PC-SPES, a supplement which induced responses but was found to contain warfarin and estrogen, highlight the need for content verification. The measurement of testosterone and DHT levels during our study is another strength, as we sought to identify an active agent without the hormonal effects of ADT. Weaknesses include the lack of a placebo control and the modest sample size.

Concerns raised by the SELECT trial about potential negative impact of vitamin E on prostate cancer incidence and selenium on diabetes risk could be viewed as a weakness of the composition of PHC. However, it should be noted that the combination arm of the SELECT trial showed no increased risk, suggesting potential differences related to combining vitamins and micronutrients. Also, the physician’s health study II did not find any difference in risk of incident prostate cancer with vitamin E supplementation. Importantly, both of these studies were performed in the setting of primary prevention: there could be differential effects of micronutrients on normal or precancerous cells as compared with effects on established cancer cells. Epidemiological studies of serum vitamin D levels have reported conflicting data, and ultimately both high and low vitamin D levels may be associated with higher prostate cancer risk. The relatively low level of vitamin D contained in PHC is unlikely to push subjects into a high risk category. However, again it must be noted that these data may not applicable to a population of patients who already have prostate cancer.

We found striking in vitro activity of PHC in both androgen-dependent and -independent prostate cancer cell lines and confirmed that activity in a prospective single-arm trial. One limitation is that in vivo vitamins and other components of PHC are likely metabolized, thus the direct effect of the compound may not translate to clinical benefit. The in vitro suppression of AR we identified after in vitro exposure to PHC cannot be explained by changes in circulating testosterone or DHT levels, and clinically patients were not found to have changes in circulating androgen levels, nor did they report typical side effects of hypogonadism (hot flashes, mastodynia). The AR belongs to the nuclear receptor superfamily and functions as a ligand-dependent transcription factor, binding to the androgen-responsive element and recruiting co-regulatory factors. Further work will be needed to understand how PHC suppresses AR expression.

Our study is not the first to evaluate a natural supplement in men with BCR prostate cancer. Pomegranate juice and extract have both been shown to influence PSA DT as well as induce PSA declines in 13–35% of patients treated. Perifosine, studied by the California Cancer Consortium, induced PSA declines in 5 of the 24 subjects, though none had a >50% PSA decline. Cross-trial comparison is difficult, given the known prognostic influence of PSA DT and Gleason scores. In the pomegranate juice study, there were no patients with Gleason >7, whereas in our study 23% of patients had Gleason 8–10 cancer; the PSA DT at baseline in the pomegranate juice study was 14 months, whereas in our population it was 9.4 months. There was no indication of how many men had received ADT in the pomegranate study; this clinical variable could also confound outcomes, and of note, none of these trials utilized placebo control. The completion of multiple clinical trials utilizing non-hormonal agents for BCR prostate cancer indicates major interest in this approach.

The median time to metastasis was relatively short in our population, likely reflecting the inclusion of more aggressive populations, including those with PSA DT between 3 and 6 months, high Gleason scores and previous treatment with ADT for BCR. It should also be taken in context that this figure is from study entry rather than from time of BCR, as in published reports which found median time to metastasis of 8 years, in order to be eligible, our patients had to have a PSA level of at least 1, and many started with higher PSA levels, representing a variable number of years since meeting the definition of BCR. In order to better determine the impact of PHC and other supplements in BCR, randomized, placebo-controlled trials are needed with clinically meaningful end points such as time to metastasis. One meta-analysis of single-arm studies of non-hormonal biological therapies (including lenalidomide and marimistat) in men with BCR found correlation between changes in PSA DT and metastasis-free survival. This provides rationale to conduct randomized, placebo-controlled trials of PHC or other supplements with an end point of metastasis-free survival.

Better prognostic markers are needed for men with BCR. CTCs have strong, independent prognostic value in the setting of metastatic, castration-resistant prostate cancer. However, their utility in patients with BCR is unproven. One limitation for the use of CTCs is that, in earlier stage prostate cancer is low yield; one study detected CTCs in only 3 of the 36 men (8.3%) with BCR prostate cancer using the Veridex platform. Using parylene membrane filters, we identified CTCs in nearly half of our population and noted changes in CTC counts during treatment, though our numbers were too small to allow correlation with clinical benefit. If additional studies identify an association between CTC and time to metastasis, this marker could provide valuable stratification for men with BCR. Men predicted to have shorter time to metastasis could be enrolled on clinical trials of early aggressive interventions, creating an enriched population to enhance the likelihood of obtaining significant results. In addition, more studies are needed to discover predictive biomarkers of response to PHC, to identify patients most likely to benefit.

CONCLUSION

Although the study did not meet its primary end point of 50% PSA declines, we found that PHC, a combination herbal supplement, induced some PSA declines in men with BCR prostate cancer, without reducing serum androgens. There were few, transient adverse events. Additional study of this agent in a placebo-controlled trial is planned.

CONFLICT OF INTEREST

Dr Pinski holds the patent for Prostate Health Cocktail and has commercial interest in the company that distributes it, OncoNatural Solutions. The other authors declare no conflict of interest.

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