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Abstract: *Dietary intake of lycopene and soy has been associated with a lower risk of prostate cancer. In vitro studies with lycopene and genistein, a soy isoflavone, have shown induction of apoptosis and inhibition of cell growth in androgen-sensitive (LNCaP) and androgen–independent (PC3 and VeCaP) prostate cancer cell lines. In a previous Phase II clinical trial in prostate cancer patients, we observed prostate-specific antigen (PSA) stabilization with soy isoflavone intake. In this Phase II clinical trial, we investigated the efficacy of lycopene alone or in combination with soy isoflavones on serum PSA levels in men with prostate cancer. To be eligible for the study, men with prostate cancer had to have rising serum PSA following local therapy or while on hormone therapy. Study population included 71 eligible patients who had 3 successive rising PSA levels or a minimum PSA of 10 ng/ml at 2 successive evaluations prior to starting therapy. Subjects were randomly assigned to receive a tomato extract capsule containing 15 mg of lycopene alone (n = 38) or together with a capsule containing 40 mg of a soy isoflavone mixture (n = 33) twice daily orally for a maximum of 6 mo. One patient on the lycopene arm did not receive therapy due to his inability to ingest the study pill. There was no decline in serum PSA in either group qualifying for a partial or complete response. However, 35 of 37 (95%) evaluable patients in the lycopene group and 22 of 33 (67%) evaluable patients in the lycopene plus soy isoflavone group achieved stable disease described as stabilization in serum PSA level. The data suggest that lycopene and soy isoflavones have activity in prostate cancer patients with PSA relapse disease and may delay progression of both hormone-refractory and hormone-sensitive prostate cancer. However, there may not be an additive effect between the 2 compounds when taken together. Future studies are warranted to further investigate the efficacy of lycopene and soy isoflavones in prostate cancer as well as the mechanism of potential negative interaction between them.*

Introduction

Patients with prostate cancer who have rising serum prostate-specific antigen (PSA) after curative surgery or radiation without other clinical evidence of disease pose a therapeutic dilemma with no clearly established guidelines. Androgen deprivation therapy remains the most effective treatment, with rapid induction of a PSA response and a likelihood of delaying disease progression. The prognostic characteristics determining outcome in PSA-relapse disease are not well defined. The optimal time to start androgen deprivation therapy is also unknown. Testosterone suppression has numerous side effects including hot flashes, loss of libido, and osteoporosis leading to skeletal events. The therapy of patients with PSA-relapse prostate cancer who have failed androgen deprivation therapy represents an even larger clinical dilemma. Testing of other therapies in PSA-relapse disease has been limited by the lack of objective measurable disease and the reliance on PSA response as a therapeutic endpoint. This disease category is the current focus of therapeutic research with the hope of delaying the progression to metastatic disease and consequently prolonging survival.

A potential strategy for delaying the progression of disease in PSA-relapse patients is the use of nutritional or botanical compounds such as tomato lycopene or soy isoflavones that may have biological effects against prostate cancer. Dietary intake of lycopene has been associated with a decreased risk of prostate cancer, suggesting that lycopene may have a role in the prevention of prostate cancer (1). In addition, among prostate cancer patients, higher lycopene intake has been

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associated with lower stage of disease, suggesting that lycopene may also impede the progression of disease (1). Lycopene is a non-provitamin A carotenoid that gives tomatoes their red color. Humans and animals do not synthesize lycopene and thus depend on dietary sources. Tomatoes and tomato products, watermelon, pink grapefruit, apricots, pink guava, and papaya are the dietary sources of lycopene (2,3). Lycopene is a potent antioxidant and quencher of singlet oxygen (4,5), resulting in protection against oxidative DNA damage in vitro and in vivo [reviewed in (6)]. Evolving evidence suggests that carotenoids may modulate processes related to mutagenesis, carcinogenesis, cell differentiation, and proliferation independently of their role as antioxidants or precursors of vitamin A (7–23). The postulated possible mechanisms of action of lycopene include 1) inhibition of growth and induction of differentiation in cancer cells by modulating the expression of cell cycle regulatory proteins (12,24–27), 2) modulation of the IGF-1/IGFBP-3 system (27–36), 3) up-regulation of gap-junctional gene connexin 43 (Cx43) and increased gap junctional intercellular communication (7–11,13–20), 4) modulation of redox signaling (37), 5) prevention of oxidative DNA damage (38,39), 6) inhibition of IL-6 and androgen (40), 7) inhibition of 5-lipoxygenase (41), 8) modulation of carcinogen metabolizing enzymes (42), and 9) modulation of immune function (43).

Although there is considerable interest in the role of lycopene as a therapeutic agent in prostate cancer, only a few small clinical trials have been reported (44–46). Kucuk et al. (44) conducted a randomized 2-arm clinical trial to investigate the effects of lycopene supplementation on the cancerous and benign prostate tissues. Patients with a diagnosis of prostate cancer who were scheduled to undergo radical prostatectomy were randomly assigned to either 30 mg of oral lycopene supplementation or no intervention for 3 wk prior to surgery. Kucuk et al. (44) reported that the plasma PSA level decreased by 18% in the intervention group ($n = 15$), whereas it increased by 14% in the control group ($n = 11$) over the study period ($P = 0.22$). Chen et al. (45) and Ansari and Gupta (46) have also reported a PSA response to lycopene supplementation in patients with prostate cancer.

Soy has also been of interest in the prevention and therapy of prostate cancer. Epidemiologic studies have shown an inverse association between soy consumption and prostate cancer risk (47–50). Isoflavones have been suggested as the principal chemical constituents responsible for the potential preventive effect of soy against prostate cancer (51). In some Asian countries with high soy consumption, the incidence of latent and small prostate carcinomas is the same as in Western countries, whereas the mortality from clinically diagnosed prostate cancer is lower (52), suggesting that soy isoflavones may also inhibit the progression of prostate cancer. A variety of possible mechanisms have been proposed for the activity of soy isoflavones in prostate cancer, which include estrogen-like effects (53), prevention of oxidative DNA damage (54,55), reduction in cancer cell proliferation (56), inhibition of angiogenesis (57), modulation of steroid-metabolizing enzymes (58), tyrosine kinase (59) and topoisomerase II (60), and effects on signal transduction molecules (61).

We have previously reported the results of a pilot study with soy isoflavones in patients' prostate cancer who had rising serum PSA levels (62). Patients were enrolled on the study if they had either newly diagnosed and untreated disease under watchful waiting with rising PSA (Group I) or had increasing serum PSA following local therapy (Group II) or while receiving hormone therapy (Group III). The study intervention consisted of 100 mg of soy isoflavone taken by mouth twice daily for a minimum of 3 or maximum of 6 mo. Although there were no sustained decreases in PSA qualifying for a complete or partial response, stabilization of the PSA occurred in 83% of patients in hormone-sensitive (Group II) and 35% of hormone-refractory (Group III) patients. There was a decrease in the rate of the rise of serum PSA in the whole group ($P = 0.01$), with rates of rise decreasing from 14% to 6% in Group II ($P = 0.21$) and from 31% to 9% in Group III ($P = 0.05$) following the soy isoflavone intervention. These data suggest that soy isoflavones may have an antitumor effect in patients with prostate cancer.

Because our previous clinical trials suggested clinical activity of lycopene (44) and soy isoflavones (62) in patients with prostate cancer, we conducted a Phase II prospective randomized study to evaluate the efficacy of lycopene alone or in combination with soy isoflavones.

Methods

Patient Eligibility

Eligible patients had to have histologically proven prostate cancer with PSA progression. Patients did not have to have clinical evidence of metastatic disease to be eligible. All patients had to be off any other therapy for prostate cancer, except for the patients who were already on luteinizing hormone releasing hormone analogue were required to continue taking it. Patients had to demonstrate a rising trend with 3 successive elevations at a minimum interval of 2 wk or at least 2 PSA values at least 2 wk apart with a minimum PSA of 10 ng/ml. Patients had to be off flutamide and any other hormones including steroids for at least 4 wk and off bicalutamide for at least 6 wk. A minimum of 4 wk since prior radiation therapy or chemotherapy was required. Patients taking other supplements, such as soy, vitamin E, lycopene or selenium, were not eligible to participate. Patients were allowed to take a single standard dose multivitamin daily, if they wished. Patients had to have a life expectancy of more than 12 wk and a performance status of 0 to 3 by Southwest Oncology Group criteria (63). There were no eligibility restrictions based on organ function. All patients had to sign an informed consent form in accordance with Wayne State University Human Investigations Committee. Based on prior therapy, patients were stratified into 2 groups: 1) PSA progression without administration of hormone therapy

(hormone sensitive relapse) and 2) progression on prior hormone therapy (gonadotropin-releasing hormone agonist). There were no patients with previous chemotherapy.

Treatment Plan

The protocol therapy consisted of either lycopene (Lyc-o-mato®) at a dose of 15 mg orally twice daily or a combination of lycopene at the same dose and isoflavone (Solgen®) at a dose of 40 mg orally twice daily for a maximum of 6 mo. Lycopene (Lyc-o-mato) and soy isoflavone (Solgen) capsules were provided by LycoRed Company, Beer-Sheva, Israel. To verify compliance, patients were given a medication calendar and were asked to check the appropriate boxes when they take the study tablets. A pill count on returned bottles was made and compared to the calendar. Patients taking less than 75% of the prescribed dose were to be counseled to practice stricter compliance. If on the next monthly visit there was a similar finding, then the patient was to be taken off protocol.

Clinical Evaluations for Toxicity and Response Assessment

Toxicity and response were evaluated monthly. Toxicity was graded using the National Cancer Institute Common Toxicity Criteria, CTC version 2.0 (64). Response was assessed according to the PSA working group guidelines (65). If patients had metastatic disease, scans were performed every 3 mo while on study. Severe adverse effects were monitored and reported according to the Wayne State University Investigational Review Board toxicity reporting guidelines. In addition to a history and physical examination, baseline assessments included complete blood count with differential count, blood chemistry profile (SMA-12), serum electrolytes, and testosterone levels. These were repeated at the end of the 1st mo and at 3 and 6 mo. Serum PSA levels were measured at baseline and monthly while on study. All patients were required to have baseline radiologic evaluation, including bone scans and CT scan of the abdomen and pelvis prior to enrollment, for disease assessment, and these were repeated if clinically indicated.

Complete PSA response (CR) was described as normalization of PSA (<4 ng/ml except for patients with history of radical prostatectomy in which normalization =<0.4 ng/ml) sustained for 3 successive determinations minimum 2 wk apart. Partial response (PR) was defined as $\geq$50% reduction of PSA sustained for at least 2 successive determinations minimum 2 wk apart. Progressive disease (PD) was defined as 2 PSA values at least 2 wk apart with >50% increase over the minimum PSA level observed during the study. Stable disease (SD) was defined as PSA value changes, which do not qualify for CR, PR, or PD (65).

Statistical Methods

Linear mixed-effects modeling was used to test the hypotheses that treatment with lycopene or a combination of lycopene and soy reduces the rate of PSA rise in patients with prostate cancer. Logarithm of PSA was used to achieve better model fit. Analyses were stratified by prior hormone therapy (i.e., hormone sensitive or hormone resistant disease). PSA measurements within 1 yr prior to intervention were analyzed as baseline levels. Only the PSA measurements within the maximum treatment time of the 6-mo study period were analyzed as postintervention data. Patients in our study had different numbers of repeat PSA measurements, and all patients did not have their PSA levels measured at precise intervals. Mixed-effects models provide a useful alternative to classical multivariate regression techniques for modeling such data. All analyses were performed using PROC MIXED in SAS, version 9.1 (Cary, NC).

Primary endpoint was serum PSA. Based on our previous studies (44,62), we anticipated a study population of 60 evaluable patients would provide adequate data to determine significant effect. We entered 71 patients to accommodate a noncompliance rate of approximately 15%.

Results

Patient Characteristics

A total of 71 patients with prostate cancer and rising PSA were enrolled; 38 patients were randomized to the lycopene alone arm (L), and 33 patients were treated with the combination of lycopene and isoflavone (L+I). Patient characteristics are shown in Table 1. The median age was 75 yr, and the median PSA was 6.5 ng/ml. A total of 47 patients (66%) were White and 21 (30%) patients were African American. A total of 25 patients (35%) had progressed on hormone therapy, 18 patients (25%) had detectable metastatic disease, and 58 patients (75%) had PSA only disease.

Treatment Administration and Toxicities

Out of the 71 enrolled, 70 received therapy. One patient randomized to the lycopene alone arm refused therapy,

Table 1. Patients Characteristics ($N = 71$)[a]

Patient Characteristics	Lycopene, $n = 38$ (53.5%)	Lycopene+Isoflavone $n = 33$ (46.5%)
Median age, yr Range	73 (57–89)	76 (50–91)
Race		
White	24 (63%)	23 (70%)
African American	12 (31%)	9 (27%)
Other	2 (6%)	1 (3%)
Prior systemic therapy		
Hormones	14 (36%)	11(33%)
None	24 (64%)	22 (67%)
Presence of metastases		
Present	8 (21%)	10 (30%)
Absent	30(79%)	23 (70%)
Median PSA (range)	6.1 ng/ml (1.1–147 ng/ml)	6.9 ng/ml (0.8–60.9 ng/ml)

a: Abbreviation is as follows: PSA, prostate-specific antigen.

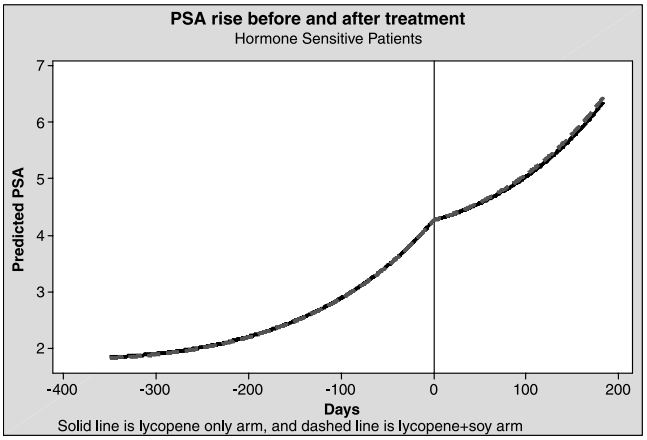

Figure 1. Serum prostate-specific antigen (PSA) levels of hormone-sensitive study subjects before and after they start taking the study supplements.

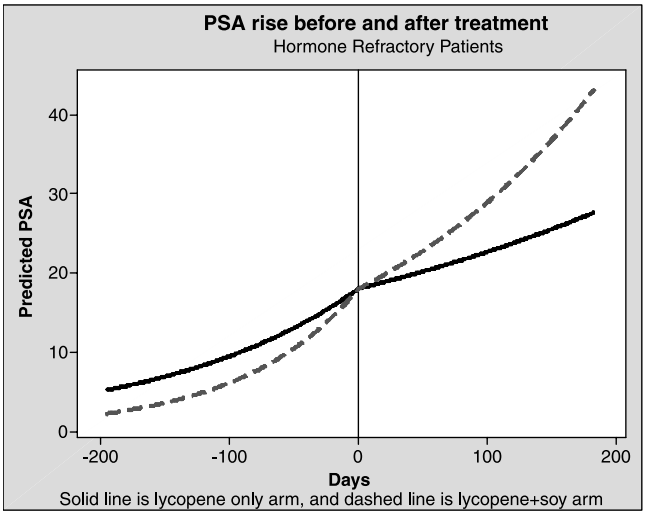

Figure 2. Serum prostate-specific antigen (PSA) levels of hormone-refractory study subjects before and after they start taking the study supplements.

stating that he was unable to swallow the pills. A total of 23 patients (60%) in the L arm and 16 patients (48%) in the L+I arm completed the planned 6 mo of therapy. The only reason for discontinuing therapy was PSA progression. Median duration of therapy was 6 mo in the L arm and 5.5 mo in the L+I arm. No significant treatment-related toxicities were observed. Both regimens were exceedingly well tolerated, with only 1 patient reporting a Grade 1 headache that was possibly related to therapy.

Response

No objective partial or complete PSA responses were noted. However, PSA stabilization as described previously for a minimum of 3 mo was observed in 35 (95%) of the 37 evaluable patients on L arm versus 22 (67%) of the 33 evaluable patients on L+I arm. Overall, there was a significant rise in PSA over time ($P = 0.0001$) for the hormone refractory as well as the hormone sensitive patients. In both therapeutic arms, there was a significant decline in the rate of PSA rise from pretherapy to posttherapy ($P = 0.015$ in the hormone sensitive group, and $P = 0.017$ in the hormone refractory group; Figs. 1 and 2). However, for patients in the hormone sensitive group, there was no significant difference in the decline rates between the lycopene only arm and the combination arm. In the hormone refractory group, patients treated with lycopene only had significantly greater decline in the PSA rate of rise from pretherapy to posttherapy compared to patients treated with the combination of lycopene and soy ($P = 0.02$).

Discussion

Lycopene and soy isoflavones are dietary compounds, and their therapeutic application is attractive to patients with advanced prostate cancer who may not be candidates for standard therapy due to advanced age, indolent disease, and/or comorbid conditions. Furthermore, a substantial number of patients with PSA relapse disease are reluctant to start androgen deprivation therapy because of potential side effects such as erectile dysfunction, hot flashes, and osteoporosis. In hormone refractory patients, chemotherapy is indicated; however, the benefit of chemotherapy is of limited duration, and the side effects are substantial. Therefore, the idea of using nutritional compounds to delay androgen ablation therapy in androgen-dependent disease and to delay chemotherapy in androgen-independent disease has substantial merits. The results of our previous pilot trials showed that lycopene and isoflavones are safe, well accepted, and well tolerated by prostate cancer patients. In addition, they have demonstrated preliminary evidence of antitumor effect. This study was conducted to investigate the efficacy of lycopene alone or in combination with soy isoflavones in patients with hormone sensitive or hormone refractory prostate cancer who have rising serum PSA. Although there were no objective (partial or complete) PSA remissions in this study, a decline in the rate of PSA rise was observed in both arms of the study. Particularly, lycopene administration slowed the rate of PSA progression in both hormone-sensitive and hormone-refractory patients.

There have only been a few small previous clinical trials with lycopene (44–46). Kucuk et al. (44) reported that the plasma PSA level decreased by 18% in 15 patients with prostate cancer who were given 30 mg of lycopene for 3 wk prior to radical prostatectomy. Interestingly, in the lycopene group, 11 of 15 patients (73%) had no involvement of surgical margins and/or extraprostatic tissues with cancer compared to 2 of 11 patients (18%) in the control group ($P = 0.02$). Kucuk et al. (44) also noted that the expression of Cx43, in the malignant part of the prostate glands, was higher in the lycopene group than the control group ($P = 0.13$). Prostatic

tissue lycopene levels were 47% higher in the lycopene group compared to control group ($P = 0.02$).

Chen et al. (45) conducted a similar clinical trial to examine the effects of consumption of tomato sauce-based pasta dishes in patients with prostate cancer. A total of 32 patients with localized prostate adenocarcinoma consumed a lycopene rich diet for 3 wk (30 mg of lycopene per day) preceding their scheduled radical prostatectomy. After the dietary intervention, serum and prostate lycopene concentrations were significantly increased. Serum PSA levels decreased from 10.9 ng/ml [95% confidence interval (CI) = 8.7–13.2 ng/ml] to 8.7 ng/ml (95% CI = 6.8–10.6 ng/ml, $P < 0.001$). Furthermore, leukocyte oxidative DNA damage was significantly reduced, from 0.61 8-OHdG/10^5 dG to 0.48 8-OHdG/ 10^5 dG ($P = 0.005$). Prostate tissue oxidative DNA damage was significantly lower in men who had consumed the lycopene-rich diet than in the randomly selected patients (0.76 8-OHdG/10^5 dG and 1.06 8-OHdG/10^5 dG, respectively; $P = 0.03$).

Ansari and Gupta (46) compared the efficacy of lycopene plus orchiectomy with orchiectomy alone in 54 patients with metastatic prostatic cancer. After 6 mo of follow-up, there was a significant reduction in PSA level in both groups but more marked in the lycopene plus orchiectomy group (mean = 9.1 and 26.4 ng/ml, $P = 0.9$). After 2 yr, these changes were more consistent in the lycopene group (mean = 3.01 and 9.02 ng/ml; $P < 0.001$). A total of 11 (40%) patients in orchiectomy and 21 (78%) patients in the lycopene plus orchiectomy group had a complete PSA response ($P < 0.05$). Bone scans showed that in the orchiectomy arm, only 4 (15%) patients had a complete treatment response, whereas in the lycopene plus orchiectomy group, 8 (30%) patients had a complete response ($P < 0.02$). Additionally, there was a significant improvement in the peak urine flow rate in the lycopene group ($P < 0.04$). A total of 12 (22%) patients in the orchiectomy group and 7 (13%) in the lycopene group died of prostate cancer ($P < 0.001$).

Clark et al. (66) conducted a Phase I-II trial of lycopene supplementation in 36 men with biochemically relapsed prostate cancer after definitive local therapy. A total of 6 consecutive cohorts of 6 patients each received daily supplementation with 15, 30, 45, 60, 90, and 120 mg/day for 1 yr. The primary endpoints were PSA response (defined as a 50% decrease in serum PSA from baseline), pharmacokinetics, and the toxicity/tolerability of the regimen. No serum PSA responses were observed, and 37% of the patients had PSA progression. The plasma levels of lycopene were similar for a wide dose range (15 to 90 mg/day) and reached a plateau by 3 mo. This study suggested that lycopene supplementation might not result in a PSA response. Future studies may use PSA stabilization or PSA doubling time instead of PSA-response as an endpoint.

In addition to lycopene, there has been considerable interest in potential uses of soy isoflavones in patients with prostate cancer. We previously conducted a pilot study in patients with prostate cancer who had rising serum PSA levels. The study intervention consisted of 100 mg of soy isoflavone taken by mouth twice daily for a minimum of 3 or maximum of 6 mo. A total of 41 patients were enrolled who had a median PSA level of 13.3 ng/ml. Although there were no sustained decreases in PSA qualifying for a complete or partial response, stabilization of the PSA occurred in 83% of patients in hormone-sensitive and 35% of hormone-refractory patients. There was a decrease in the rate of the rise of serum PSA in the whole group ($P = 0.01$), with rates of rise decreasing from 14% to 6% in hormone-sensitive patients ($P = 0.21$) and from 31% to 9% in hormone-refractory ($P = 0.05$) patients following the soy isoflavone intervention. These data suggest that soy isoflavones may benefit some patients with prostate cancer.

DeVere-White et al. (67) conducted a study to determine whether a soy isoflavone extract would lower PSA levels more than 50% in patients with prostate cancer. An open-label pilot study was conducted for 6 mo in which the patients ($n = 62$) took capsules containing the genistein-rich extract 3 times daily by mouth. The subjects were in 1 of 5 groups: after radical retropubic prostatectomy ($n = 9$), after radiotherapy ($n = 17$), after both radical retropubic prostatectomy and radiotherapy ($n = 6$) off-cycle during hormonal therapy (intermittent hormones; $n = 14$), or active surveillance ($n = 16$). Of the 62 men enrolled, 52 were available for evaluation at 6 mo. Three patients discontinued because of adverse events (diarrhea) and 7 because of personal choice. One of 52 patients had a more than 50% reduction in the PSA level. An additional 7 patients had PSA reductions that were less than 50%. All 8 patients with lower PSA levels at 6 mo were in the active surveillance (watchful waiting) treatment subgroup. Repeated measure regression models allowing for correlation between initial levels and change also indicated a decline in PSA in this group compared with other groups: 0 of 52 had a complete response, 9 (17%) had a partial response, 8 (15%) had SD, and 35 (67%) had disease progression. They concluded that soy isoflavone mixture did not appear to be an effective treatment for prostate cancer when given alone. However, 8 of 13 evaluated patients in the active surveillance group had either no rise or a decline in PSA levels of less than 50%. They suggested more study of soy isoflavones for those choosing active surveillance.

In our studies, lycopene and soy isoflavones taken alone have both resulted in PSA stabilization in the majority of patients. However, in this study, we did not observe an additive effect when soy isoflavones were administered together with lycopene. To the contrary, there was a smaller effect on the PSA when lycopene and soy isoflavones were administered together compared to when lycopene or soy isoflavones were administered alone. It is unclear whether there is a negative interaction between the 2 agents when taken together.

Many cancer patients ingest multiple dietary supplements together, as they are generally perceived as safe, and they may have multiple beneficial health effects. However, the results of this Phase II trial suggest that negative interactions may occur between dietary supplements and may have an impact on efficacy. In our study, administration of lycopene as a single agent demonstrated more favorable outcome in PSA

stabilization as compared to the use of a combination of lycopene and isoflavone in hormone refractory patients. Future studies should further investigate the potential interactions between soy isoflavones and lycopene in prostate cancer because both compounds are found in the diet, and they are often taken together as supplements by prostate cancer patients.

In conclusion, the results of this Phase II randomized trial suggest that lycopene may decelerate the rate of PSA rise in relapsed prostate cancer. This trial also suggests that isoflavones in combination with lycopene may not have an additive effect. Further clinical assessment of lycopene alone or sequentially with isoflavones in relapsed prostate cancer is recommended. Future studies should also investigate the mechanism of potential negative interaction between the 2 compounds. In addition, clinical trials designed to address clinically significant endpoints such as time to progression, development of distant metastatic disease, or overall survival in PSA-relapse prostate cancer should also be conducted using lycopene as 1 of the arms. Although there was no objective PSA remission, the observed decline in the rate of PSA rise is encouraging. The efficacy of lycopene in slowing the rate of PSA progression was demonstrated in both hormone-sensitive and hormone-refractory prostate cancer. The limitations of our study include small sample size, the lack of stratification for prognostic factors, and the lack of a placebo arm. Despite the study limitations, the results provide additional rationale for future testing of lycopene in a wide spectrum of prostate cancer patients.

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