The term “complementary and alternative methods” (CAM) refers to products and regimens that individuals may employ either to enhance health and well being or to cure disease. Complementary therapies are used along with mainstream care to manage symptoms, relieve stress, and enhance quality of life. In contrast, alternative methods are used instead of evidence-based medical therapy. The dangers inherent in bogus alternatives are two-fold: First, they may cause direct harm, and second, they may be ineffective, resulting in disease progression. In this section, we hope to help providers guide patients toward CAMs that might improve quality of life and away from those that are ineffective, toxic, and wasteful of time and money.

PC-SPES: Current Evidence and Remaining Questions

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WHAT IS “PC-SPES?”

PC-SPES is a powdered herbal nutritional supplement that is marketed for “prostate health” but has been used as a complementary or alternative treatment for prostate cancer. The name of the product derives from “PC,” which stands for prostate care, and “spes,” which is the Latin word for hope.1

Originally developed in the early 1990s by Sophie Chen, PhD, currently a Professor at New York Medical College, Valhalla, NY, PC-SPES has been commercially available since 1996. The popular supplement consists of eight herbs that contain a range of biologically active phytochemicals (Table 1).

PC-SPES is available in capsule form from select distributors, health care professionals, and directly from the manufacturer. Each capsule contains roughly 320 mg of the herbal mixture.

Patients in reported clinical studies usually took the capsules twice or three times daily, with a total daily dose of six to nine capsules.1-9 One study used a protocol with doses escalating at weekly intervals, from one to three tablets, three times daily.3 A treatment plan that includes PC-SPES should be developed together by the patient and physician and should consider the possibility of herb-drug interactions.

MOVING FROM TESTIMONIALS TO CLINICAL TRIALS

Until recently, information on PC-SPES was largely limited to anecdotal reports and testimonials shared among patients in support groups and on Internet bulletin boards. Prompted by increasing patient interest and particularly their use, basic and clinical investigators have begun to study PC-SPES to determine its mechanisms of action, potential activity/efficacy, and safety in men with prostate cancer.

While some consumers and proponents of “alternative” or “natural” remedies claim that conventional practitioners are sometimes hostile toward such products, most are simply skeptical. Recent laboratory and
clinical studies of PC-SPES underscore the willingness of those in traditional medicine to investigate any promising anticancer approaches.

Most practitioners of conventional medicine believe that natural products, such as PC-SPES, should be subject to the same standards and approaches as substances that are classified as pharmaceuticals. And, for any anticancer modality to be considered for clinical use, it must compare favorably against a proven therapy in comparable groups of patients, with evidence of benefit documented by well-designed, well-conducted prospective trials.

**PC-SPES: MECHANISMS OF ACTION**

Clinically, PC-SPES has potent estrogenic activity and has been associated with significant reductions in serum levels of both testosterone and prostate specific antigen (PSA).1-9 Many of its effects and side effects are similar to those of diethylstilbestrol (DES).1-9 However, the estrogenic activity of PC-SPES appears to be due to the presence of phytoestrogens, which are chemically distinct from DES, estrone, and estradiol8 or compounds with similar structures and metabolites.

In preclinical experiments, exposure to PC-SPES increased the apoptotic rate of cultured prostate cancer cell lines, such as LNCaP, PC3, and DU145.2 Although PC-SPES produced a potent dose-dependent reduction in cellular viability and growth rates of cultures of both hormone-sensitive and hormone-insensitive prostate cancer cell lines, the former responded at much lower doses.7 Growth of prostate cancer cell lines grown as nude mouse xenografts was also inhibited.2 While the agent is active against some hormone-independent prostate cancers,2-4,6 this activity is less than in androgen-sensitive tumors. The finding that PC-SPES is active against some tumors that are refractory to estrogenic agents such as DES and estramustine suggests that estrogen-like effects are not its sole mechanism of action.4

Reduction of pain in men with prostate cancer appears primarily related to the direct antitumor effect of PC-SPES. Nevertheless, at least one group has suggested that four components of PC-SPES—Glycyrrhiza glabra, Ganoderma lucidum, Rabdosia rubescens, and Panax pseudoginseng—are also known to have both anti-inflammatory and analgesic properties.6

In summary, although research to date—both preclinical and clinical—indicates that PC-SPES acts primarily as a phytoestrogen, other components may exert therapeutic effects via mechanism(s) of action that remain essentially unknown.

### EFFICACY

Hormonal therapies (LHRH analogs, anti-androgens, or orchiectomy) are the mainstay of treatment for advanced prostate cancer.

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**TABLE 1**

| PC-SPES: Ingredients |
|-----------------------|
| Chrysanthemum mori folium (Mum, Chu-hua) |
| Ganoderma lucidum (Reishi Mushroom, Ling zhi) |
| Glycyrrhiza Glabra and Glycyrrhiza Uralensis (Licorice) |
| Isatis indigotica Fort (Dyers Woad, DaQing Ye) |
| Panax Pseudo-Ginseng (San Qi) |
| Rabdosia rubescens (Rubescens, Dong Ling Cao) |
| Scutellaria baicalensis Georgi (Baikal Skullcap, Huang-chin) |
| Serenoa repens (Saw Palmetto) |
Although androgen-dependent disease may be successfully managed for limited periods, most prostate cancers eventually become refractory to such hormonal manipulation. The currently available options for advanced androgen-independent prostate cancer are of limited efficacy. When the disease continues to progress despite androgen ablation, overall prognosis is poor.

In this context, both patients and clinicians have been eager to determine whether use of PC-SPES, either as a single agent or combined with conventional therapies, can significantly and safely impact progression of advanced disease beyond that which is achievable with conventional treatments. Currently available published data summarizing PSA response rates among men with hormone-sensitive (or hormonal therapy-naïve) and hormone-independent tumors are shown in Table 2.

**Early Studies**

A study of PC-SPES in eight patients with hormone-sensitive prostate cancer reported in 1998 indicated that both serum PSA and testosterone were significantly decreased; the authors warned that use of the herbal mixture by patients could confound results obtained with conventional or investigational therapies. At about the same time, another group of investigators conducted a prospective study of PC-SPES in 33 men with prostate cancer who had either refused conventional therapy or whose previous treatment (surgery, radiotherapy, cryosurgery, hormones) had failed. While the investigators observed similar reductions in serum PSA levels, they also noted that there were no overt clinical signs of disease progression (increased bone pain, local recurrence presenting as urinary obstruction, or positive bone scans) in any patient during the study, which had a mean follow-up of 6.8 months (range, two to 24 months).

In 1999, USToo International, a prostate cancer support group, published results of a survey of its members showing that 77% of 102 respondents reported beneficial effects with PC-SPES. A more detailed online posting of the results reported that 94% of respondents had reduced or stable PSA levels. Such findings prompted other investigators to initiate additional studies of the supplement.

All clinical studies of PC-SPES in prostate cancer patients to date have reported decreases in serum PSA levels and a few have documented quality of life improvements.

**Hormone-Refractory Prostate Cancer**

Pfeiffer et al. treated men with metastatic hormone-refractory prostate cancer using PC-SPES (three capsules three times daily, or a total of 2.88 g/day) for five months. The men also received androgen-ablation therapy for the duration of the study to avoid the known effects of anti-androgen withdrawal on PSA levels.

Thirteen of these 16 hormone-refractory patients, including some whose cancers had progressed during treatment with estrogens, had a greater than 50% reduction in serum PSA levels. Additionally, most patients reported pain relief, better ambulation, more energy, and increased appetite, all contributing to overall improvement in quality of life. These investigators could not predict the duration of these effects because of the short-term study design.

These findings and conclusions were confirmed in a larger study of 69 patients with prostate cancer who were divided into three groups: Those who had received prior therapy (e.g., surgery, radiation, hormone, cryotherapy); those who had received prior hormonal therapy and were experiencing recurrence; and those with localized, untreated disease. At eight and a half months median follow-up,
none of the patients exhibited overt signs of disease progression, and more than two-thirds had a lower level of serum PSA at each follow-up period compared with pre-PC-SPES levels. Moreover, the authors observed that a large proportion of patients (74% at six months) with hormone-refractory prostate cancer had decreased PSA levels at different follow-up times and suggested that the estrogen-like activity of PC-SPES may not be its sole mechanism of action.²

Small et al. undertook a study of the herbal supplement in 33 hormone-sensitive and 37 hormone-refractory patients.³ Although, not surprisingly, responses were much more vigorous in the androgen-dependent group—100% of patients experienced a PSA decline of 80% or more—more than half of those with androgen-independent disease also responded to treatment with the supplement (54% experienced a PSA decline of 50% or more). These authors reported a PSA decline of 50% or more among half of the androgen-independent patients who had developed progressive disease despite previous second-line hormone therapy with ketoconazole. In addition to documenting these PSA responses, bone scans were serially observed. Among 25 men with documented bone metastases from hormone-refractory cancers, lesions remained stable in seven and improved in two during treatment. Whether these effects exceed those expected with estrogens, they concluded, requires further investigation.

Oh et al.⁴ recently reported that 23 men with androgen-independent prostate cancer experienced a 40% median decline in PSA level after treatment with PC-SPES overall, and that more than half of the patients had a greater-than-50% decline. Some patients had received prior estrogenic therapy, including DES and estramustin, and still subsequently demonstrated a response to PC-SPES. These investigators are currently conducting a Phase II clinical trial that will randomly assign half of 108 men to an estrogen regimen and half to PC-SPES for as long as each agent reduces PSA levels. As soon as the effect stops, par-

| Authors          | AD or HN | No. with >50% PSA decrease | Percent with >50% PSA decrease | AI | No. with >50% PSA decrease | Percent with >50% PSA decrease |
|------------------|----------|----------------------------|--------------------------------|----|---------------------------|-------------------------------|
| DiPaola et al.⁵  | 8        | 5                          | 62.5                           | —  | —                         | —                             |
| Pfeifer et al.⁶  | —        | —                          | —                              | 16 | 13                        | 81                            |
| de la Taille et al.² | 28    | 19                         | 68                             | 15 | 6                         | 40                            |
| Small et al.³     | 33       | 33                         | 100                            | 35 | 19                        | 54                            |
| Oh et al.⁴        | —        | —                          | —                              | 23 | 12                        | 52                            |
| Total             | 69       | 57                         | 83                             | 89 | 50                        | 56                            |

AD: androgen dependent; HN: hormonal therapy-naïve; AI: androgen independent

Most of these studies reported the percentage of patients whose PSA levels decreased by more than 50% at some point during treatment with PC-SPES. de la Taille et al.² reported the percentage of patients showing a greater than 50% reduction at several follow-up periods after starting treatment. The six-month time point was selected for this table.
participants are switched to the other treatment. Any additional benefit of PC-SPES will be observable if PSA levels continue to drop after the switch from estrogen.

“NATURAL” DOES NOT NECESSARILY MEAN “SAFE”

Any physiologically active substance, whether synthesized and manufactured or naturally occurring, has the potential to cause adverse effects. As PC-SPES is a complex mixture with multiple components, the potential for inducing side effects is considerable.

Most investigators characterize the side effects associated with PC-SPES as mild, and the regimen as well tolerated. As with androgen deprivation or estrogenic therapy, men who take PC-SPES may experience gynecomastia (breast enlargement), nipple tenderness, decreased libido, hot flashes, and erectile dysfunction. Other reported side effects included leg cramps, nausea, and diarrhea (Table 3).

The most serious potential adverse effects are thromboembolic events, such as deep vein thrombosis, phlebitis, or pulmonary emboli, although these seem to occur less frequently than with DES. Moreover, investigators point out that prostate cancer patients seem to be at increased risk of hypercoagulable events, regardless of therapy. Nevertheless, until further studies rule out such risk, PC-SPES should not be considered safe for men with histories of cardiovascular or thromboembolic disease.

Despite patient instructions warning that PC-SPES not be combined with other medications, it is likely that some men may use the supplement without informing their physicians, potentially confounding results of clinical trials. An herbal mixture such as PC-SPES may contain literally hundreds of unique compounds, making it difficult to identify active agents and sharply increasing the potential for serious interactions with other herbs, medications, vitamins, and even foods.

COST

The cost of treatment with PC-SPES is not inconsequential and is generally higher than that of treatment with DES. A one-month supply of PC-SPES for a patient taking six capsules daily, for example, costs about $325. If nine capsules daily are used, the cost is about $486. As an herbal supplement, PC-SPES would not be covered by most prescription plans and represents a substantial out-of-pocket expense for most patients. In research clinical trials, the cost of PC-SPES is covered.

| Authors            | Breast Tenderness | Nausea | Diarrhea | Fatigue | Gynecomastia | Leg Cramps and/or Swelling | Angina | Hot Flushes | Thrombosis |
|--------------------|-------------------|--------|----------|---------|--------------|---------------------------|--------|-------------|------------|
| DiPaola et al.     | 100               | —      | —        | —       | —            | —                         | —      | —           | 13         |
| Pfeifer et al.     | 38                | —      | —        | —       | —            | —                         | —      | —           | 6          |
| de la Taille et al.| 42                | —      | —        | —       | 8            | —                         | —      | 7           | 2          |
| Small et al.       | 97                | 15     | —        | 17      | —            | 69                        | —      | 42          | 4          |
| Oh et al.          | 35                | 22     | 13       | 9       | 9            | 4                         | 4      | 0           | 0          |

TABLE 3

Percent of Patients Reporting Side Effects with PC-SPES
CONCLUSIONS

Clinical studies have demonstrated that PC-SPES is an active agent against androgen-dependent and androgen-independent prostate cancer. Recent studies and clinical trials have begun to look at the herbal product's in vitro activities, its mechanisms of action, its clinical efficacy, and its associated toxicities. Despite these studies, however, much is still unknown about PC-SPES. We do not completely understand how the supplement works, which ingredients or combinations are active, or how PC-SPES influences the clinical outcomes of men with prostate cancer.

Clinical trials are underway to determine whether PC-SPES has any advantage over DES for hormone-independent prostate cancer. As yet, however, there are no prospective data demonstrating any significant benefit compared with standard therapies.

Even if PC-SPES were to prove only equivalent to conventional hormonal regimens, a lower toxicity profile would be considered an advantage. However, the comparative toxicities of PC-SPES vis-à-vis currently used pharmaceutical agents have not been sufficiently evaluated.

If PC-SPES were eventually to have a role in the treatment of men with prostate cancer, it would most likely be in the setting of hormone-refractory disease, where conventional options are limited. At this time, most experts agree that for patients with hormone-dependent prostate cancer, conventional approaches still offer the best chance of survival with good quality of life.

Although alternative treatments for cancer are rarely evaluated in the same way as pharmaceuticals, PC-SPES may serve as a model for future scientific investigations. Concerns over the limited data on herbal therapies such as PC-SPES are summarized in an editorial comment written by Ian Thompson, Jr., MD.

“If this agent had undergone appropriate testing by a pharmaceutical manufacturer we would know an appropriate dose, have a tailored combination of agents, and have detailed information regarding side effects and methods to possibly prevent them. Because of the lack of regulation of agents such as these, physicians and patients must take the place of the agency that provides oversight for regulated pharmaceuticals.”

Despite the many remaining unanswered questions about this popular alternative therapy, one thing is clear and cause for optimism: When proponents of alternative therapies and mainstream researchers work together, patients can benefit.

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