# PC-SPES, a dietary supplement for the treatment of hormone-refractory prostate cancer

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- **Objective** To assess the effectiveness of PC-SPES, a dietary supplement containing eight herbal extracts, which is a popular alternative therapy among patients with hormone-refractory prostate cancer; anecdotal reports claim that this agent provides relief of metastatic pain, improvements in quality of life and reduction of prostatic specific antigen (PSA) level.
- Patients and methods Sixteen men treated for advanced metastatic prostate cancer (stage D3) with either orchidectomy or a luteinizing-hormone releasing hormone agonist, with or without anti-androgen, were enrolled into a prospective clinical trial to evaluate the possible toxic and beneficial effects of PC-SPES. After hormone-ablative therapy had failed, and with established disease progression, all patients received supplemental treatment with PC-SPES

# Introduction

The incidence of prostate cancer has risen dramatically in recent years and will continue to rise as the population ages. In 1998, an estimated 185 000 new cases were reported in the USA alone, with  $\approx$ 42 000 deaths from prostate cancer [1]. Up to half of men with prostate cancer will eventually develop incurable disease [2] and of these patients, 10–20% will have distant metastasis on initial presentation [3].

Current therapies for newly diagnosed prostate cancer include observation, prostatectomy, radiation therapy, cryotherapy, and/or hormonal therapy. The choice of treatment is dictated by the patient's PSA level, grade and stage of the tumour, and overall health. Once the disease has spread there is no cure. Hormonal therapy with orchidectomy or an LHRH agonist with or without antiandrogen offers limited tumour suppression, ranging from months to several years. Long-term responses are uncommon and most prostate cancers become hormonerefractory. Multiple salvage regimens for this condition are under investigation, but none of the clinical trials so far has reported significant benefit or curative effects. (2.88 g daily) for 5 months. Hormonal therapy was continued throughout the trial to avoid the known withdrawal effect of anti-androgen on PSA levels.

- **Results** The supplemental intake of PC-SPES was associated with significant (P < 0.05-0.01) improvements in quality-of-life measures, reductions in patient's pain ratings (P < 0.05-0.01), and a decline in PSA levels (P < 0.01), with no major side-effects.
- **Conclusions** These results support the anecdotal reports of the beneficial effects of PC-SPES as a comparable alternative to current management regimens in hormone-refractory prostate cancer. However, no conclusions can be drawn about the long-term effects of this new herbal therapy.
- Keywords Herbal therapy, hormone-refractory prostate cancer, PC-SPES, pain, PSA

However, within these trials the end-point of partial PSA response rates (>50% decline in PSA) has expanded to include the assessment of the patient's quality of life.

Because current medical therapies for hormonerefractory prostate cancer have a variety of unpleasant side-effects and are generally ineffective, many of these patients seek alternative means of therapy. A new herbal product, PC-SPES, is currently receiving widespread attention among such patients. PC-SPES is available as a dietary supplement and consists of extracts from eight herbs: Chrysanthemum morifolium, Ganoderma lucidum (a root fungus), Glycyrrhiza qlabra (Spanish liquorice), Isatis indigotica, Panax pseudoginseng, Rabdosia rubescens, Scutellaria baicalensis and Serenoa repens (saw palmetto) [4]. There are numerous anecdotal reports claiming that this compound decreases PSA levels and relieves the pain from metastases, with no major side-effects. Many patients throughout the USA and Europe are now taking PC-SPES as a supplement or alternative to their traditional therapy, despite there being little clinical data for its efficacy and safety. Most of the presently available scientific information about PC-SPES has been derived from in vitro studies. Within these studies, PC-SPES was found to exert cytotoxic and cytostatic activity against several tumour cell lines [4], to down-regulate the

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expression of the *bcl-2* and *bcl-6* genes [5], to suppress the expression of the androgen receptor, and to reduce the levels of intracellular and secreted forms of PSA in androgen-dependent prostate carcinoma cell lines [6].

Considering the growing use of PC-SPES among patients with hormone-refractory disease and the dismal prognosis of these patients, a clinical evaluation of the safety and efficacy of PC-SPES is urgently needed. Therefore, we assessed the effects of PC-SPES on pain, quality of life and PSA levels, and its side-effect profile, in patients with hormone-refractory disease.

## Patients and methods

From April 1997 to March 1998, 16 men (aged 49-77 years) with histologically confirmed prostatic adenocarcinoma refractory to hormone-ablative therapy, gave informed consent to enter the prospective study. Urologists and anaesthesiologists at three different clinical sites in Germany and the USA evaluated the effects of PC-SPES on pain, quality of life and PSA levels. Each patient was diagnosed by TRUS-guided prostatic biopsy. Hormone refractoriness was defined as three consecutive monthly increases in PSA levels. Disease progression was documented by MRI, CT and bone scintigraphy. All 16 patients had hormone-refractory (stage D3) disease at the beginning of the study. The initial treatment of the patients' disease included radical prostatectomy, radiation therapy and/or hormonal therapy. Once their disease progressed, all patients were placed, or continued, on androgen-ablation therapy for the duration of the study, to avoid the known effect of anti-androgen withdrawal on PSA levels. Fourteen patients received a standard drug regimen with LHRHagonist with or without anti-androgen, and two patients underwent orchidectomy (Table 1). All patients were asked to take supplemental PC-SPES (three capsules, three times daily, 2.88 g/day) for 5 months. The manufacturer of PC-SPES, (Botaniclab, Brea, CA) provided the study product.

Physical examination, blood chemistry, a complete blood count, and assessment of PSA level, pain status, quality of life and toxicity were completed for each patient before and after 4, 8, 12, 16 and 20 weeks of PC-SPES treatment. The PSA level of all patients was determined using a standard assay (Abbott Laboratories, Abbott Park, IL). The pain status was evaluated using a visual analogue scale from 0 to 10, with 0 = no pain and 10 = excruciating pain. NSAID and narcotic drug intake was monitored during the entire study to further elucidate the effect of PC-SPES on pain control. Quality-of-life changes were determined using the FACT-P (Version 3) patient questionnaire [7], which contains several sets of specific questions about physical, emotional, social and functional well-being. Each of these sets of questions was summarized by the patient as a numeric answer, with 0 indicating no effect, and 10 the maximum effect on a particular aspect of the patient's overall quality of life. Toxicity was evaluated using the South-west Oncology Group (SWOG) Toxicity Criteria [8].

The data were analysed using the Mann–Whitney rank-sum and equal-variance tests. Comparisons between the control (before PC-SPES) and after 4, 8, 12, 16 and 20 weeks of PC-SPES intake were assessed for PSA level, pain, quality of life and toxicity criteria. All data are presented as the percentage of the control value. The clinical database was provided by the study investigators.

## Results

Figure 1a shows the patients' ratings for worst, mean, least and present pain scores during treatment with PC-SPES during a 7-day period before each follow-up visit. Pain scores for each pain category significantly (P < 0.05-0.01) decreased during treatment with PC-SPES. In addition, patients who had to take narcotics or NSAIDs for pain control before the study (14 of 16) required  $\approx 40\%$  less of these analgesics after 20 weeks of PC-SPES treatment.

Figure 1b presents the effects of PC-SPES on the patients' quality of life, as the percentage change from the control. PC-SPES treatment was associated with a significant (P < 0.05 - 0.001) improvement in functional, emotional and physical well-being. The measure for

Table 1 The demographics of the study patients

Patient no.	Stage at diagnosis	Initial treatment*	Age (years)
1	D1	RP	62
2	C2	CHB	66
3	D1	ORC	62
4	D1	CHB, RT	59
5	B2	CHB, RT	57
6	C2	RP	65
7	D2	CHB	77
8	C2	RT	59
9	C2	RP	66
10	C2	RP	51
11	D2	CHB	65
12	C2	CHB	61
13	D2	CHB	71
14	D1	RP	66
15	D2	ORC, RT	49
16	D2	ORC	63

\*RP, radical prostatectomy; RT, radiation therapy, ORC, orchidectomy; CHB, complete hormonal blockade. All patients were Caucasian except no. 4 (Arabic).



social well-being did not change significantly. This improvement in the quality-of-life measures was associated with few side-effects in 15 of 16 patients. Six patients complained of mild breast tenderness, one reported dyspepsia and another with a previous history of venous thrombosis developed a recurrence.

Figure 1c shows the PSA levels during PC-SPES treatment, as the percentage change from the control. There was a very significant (P < 0.01-0.001) decline in PSA levels after PC-SPES therapy. The PSA level decreased by >50% in 13 of 16 patients, compared with the control level. The mean PSA level before PC-SPES intake was 102 ng/mL and the mean PSA nadir of 42 ng/mL was attained at 12 weeks. Five patients reached a PSA nadir at 16 weeks and three at 8 weeks. In three patients, who initially responded to PC-SPES after 4 weeks of treatment, the PSA level increased to that before treatment after 12 weeks of therapy.

#### Discussion

Patients with hormone-refractory prostate cancer are reported to have a median survival of 6–12 months [9]. Current therapeutic regimens have only shown transient palliative benefit, with no increase in patient survival [9], and most of these palliative therapies have significant side-effects. Patients with such a dismal prognosis are prone to seek alternative treatments, including herbal remedies [10]. Among such remedies, PC-SPES has gained particular popularity because there are many anecdotal reports about its benefits for patients with hormone-refractory disease. The results of the present study support these claimed benefits.

The highly significant reduction in reported pain scores and analgesic drug intake in the present patients suggests a pain-relieving effect of PC-SPES. As the product was confirmed to be free of any analgesic drug admixture, the observed pain relief is interpreted as a direct effect of PC-SPES. Four components of PC-SPES, *Glycyrrhiza glabra*, *Ganoderma lucidum*, *Rabdosia rubescens* and *Panax pseudoginseng*, are known to have anti-inflammatory and analgesic effects that could explain the >40% reduction in analgesic drug use in most of the patients. In at least three patients, a decreased volume of metastatic disease may also have contributed to the reduced analgesic drug requirement, as their repeat bone scans and CT at the

Fig. 1. The mean (SEM) percentage changes from the control (levels before PC-SPES therapy) for **a**, pain scores (green, worst; light green, mean; red, present; and light red, least), **b**, quality of life (green, functional; red, physical; and light green, emotional) and **c**, PSA levels. In **a**, paired analogue data were analysed using the Mann–Whitney rank sum test and equal variance test. For all plots, \*P < 0.05; †P < 0.01; ‡P < 0.001.

20-week follow-up showed a decline in the number of bone lesions, and reduced pelvic lymphadenopathy. Such direct antitumour effects of PC-SPES have been reported by Halicka *et al.* [4] and Hsieh *et al.* [6], who described cytotoxic effects on a variety of human tumour cell lines, resulting in retardation of cancer cell growth by  $\approx 65\%$ .

The observed pain relief reported by the present patients was associated with an overall improvement in their quality of life. Better ambulation, more energy and increased appetite were reported by 15 patients, effects that may partly be caused by the *Rabdosia rubescens* component of PC-SPES.

The side-effects from PC-SPES in the present study were similar to those described by DiPaola et al. [11], but only eight of the patients developed breast tenderness, compared with all those in the study of DiPaola et al. The reason for this discrepancy is unclear; it is possible that maintaining the present patients on hormonal therapy, and perhaps different diets of the study groups, could have contributed to this difference. For example, Chinese patients with prostate cancer, who traditionally adhere to fibre-rich and low-fat diets, rarely report breast tenderness when on PC-SPES therapy (Chen S, Wang X, personal communication). This, and that only one of the present patients developed mild dyspepsia, suggests that PC-SPES has a low side-effect profile. Some evidence for low PC-SPES toxicity can also be derived from animal experiments. Mice receiving an equivalent of >150 times the recommended human dose had no significant side-effects other than increased uterine weight [11]. The recurrent deep venous thrombosis in one of the present patients with a previous history of this disease appears to agree with a few anecdotal reports. However, it remains unclear whether PC-SPES actually causes this particular sequel, which is often observed in patients with metastatic cancer. Until a possible causal relationship can be excluded, patients with a previous history of venous thrombosis should choose preventive measures with aspirin or low-dose coumadin when taking PC-SPES.

That most of the present patients responded with a >50% reduction in their serum PSA levels indicates that PC-SPES is effective. *In vitro* studies by Hsieh *et al.* [6] suggested that PC-SPES reduces intracellular and secreted forms of PSA but until recently, there was no peer-reviewed report for this effect of PC-SPES in humans. DiPaola *et al.* [11] first showed that PC-SPES decreases PSA levels in a study of a few patients with hormone-sensitive disease. However, the patients in that study were required to discontinue any form of androgen-ablation therapy during the trial, which may have confounded the results because of the known effect of anti-androgen withdrawal on PSA levels. DiPaola *et al.* [11] also concluded from their *in vitro* experiments and

the observed side-effects in their patients that the PC-SPES effects were caused by potent oestrogenic activity of the contained phytoestrogens. This conclusion seems questionable. Considering the oestrogen receptor assay used in their experiments, the final concentration of PC-SPES in the assay was 0.5 mg/mL. In comparison, the oestradiol concentration with the same oestrogenic activity is  $2.72 \times 10^{-7}$  mg/mL, i.e. a  $\approx 1.8$  million-fold greater oestrogenic potency for oestradiol, and therefore suggesting only a weak oestrogenic effect of PC-SPES in this assay. If the mechanism of action of PC-SPES was based solely on its oestrogenic activity, then several of the present patients, who were failing oestrogen therapy, should not have responded to PC-SPES. This suggests additional mechanisms of action for PC-SPES, e.g. the down-regulation of the bcl-2 and bcl-6 genes, promoting apoptosis [4], and enhancing the immune function by activating T and B cells [5].

The duration of the PSA depressing effect of PC-SPES cannot be determined from the present study. Three patients who initially responded to PC-SPES had their PSA level return to control values at 12 weeks of follow-up, suggesting that some tumours may quickly become resistant to this herbal therapy. On the other hand, eight of the 13 who responded are still enjoying the beneficial effects of PC-SPES, long after the 20-week follow-up. It is unclear whether the observed PSA effect seen in the present patients was evidence for a reduction in tumour load, as repeat CT and bone scans were not required at the end of the study. However, the improvement in the two bone scans and CT of three patients warrants further studies of PC-SPES in the treatment of hormone-refractory prostate cancer.

In conclusion, PC-SPES significantly reduces PSA levels and the pain of metastatic disease, thereby improving patients' quality of life without the detrimental side-effects seen with other drug regimens. With no cure currently available for these patients, maintaining a good quality of life is a realistic therapeutic goal that can be achieved with the dietary supplement PC-SPES.

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