Phase I trial of PC-Spes2 in advanced hormone refractory prostate cancer

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Abstract. There are few treatment options for prostate cancer once it becomes hormone refractory, with a mean life expectancy of 9-12 months. During the period 1997-2002, a product known as PC-Spes, containing a mixture of extracts from eight herbs based on the principles of traditional Chinese medicine, was reported to inhibit prostate cancer cell growth *in vitro* and reduce PSA in patients with hormone refractory prostate cancer (HRPC). This product was withdrawn from the market in 2002 due to concerns over quality control and reported contamination with traces of warfarin, indomethacin and diethylstilbesterol. PC-spes2, manufactured by Active Botanicals Ltd. (UK) with strict, independently-conducted quality control, has demonstrated no contaminants by high pressure liquid chromatography and liquid chromatography/mass spectroscopy. This compound was investigated in a single-centre, prospective, open pilot study. Eighteen patients with HRPC, mean age 72, median Gleason sum 8 (range 4-9) and median PSA 110 (range 4-2870) with three consecutive monthly increases in PSA were studied. Ten patients withdrew during the study period with significant diarrhoea (8 out of the first 10 patients at one month and only 2 out of the last 8 due to an improved dosing schedule). At one month, 7 out of 10 patients had a drop in their PSA doubling time or PSA velocity, which was still apparent in 4 out of 5 patients still on trial at three months and all three patients still on trial at six months. No serious adverse events or derangement of coagulation were observed. PC-Spes2 offers renewed hope and a safe alternative treatment option for patients with advanced HRPC. Further investigation with phase II trials is warranted.

Introduction

PC-Spes, a herbal preparation based on traditional Chinese medicine, gained popularity at the turn of the century as one the best prospects of an alternative treatment for prostate cancer, only to be withdrawn from the market in 2002 amid allegations of contamination and product inconsistencies. Made of a combination of seven Chinese herbs (*Isatis indigotica, Glycyrrhiza glabra, Panax pseudo-ginseng, Rabdosia rubescens, Dendranthema morifolium, Scutellaria baicalensis* and *Ganoderma lucidum*) and saw palmetto, PC-Spes was first marketed by Botaniclabs (Brea, CA, USA) in 1996. Numerous studies showed PC-Spes to have a dose and time-dependent anti-tumor action in both androgen-sensitive and androgen-independent prostate cancer cell lines *in vitro* and *in vivo* via a combination of reduced proliferation, apoptosis and cell cycle arrest (1-4). Subsequent trials also confirmed the clinical efficacy of PC-Spes in patients with androgen-sensitive and androgen-independent, or hormone refractory prostate cancer (HRPC). Small *et al,* found all 32 (100%) patients with hormone sensitive disease had a drop in PSA of >80%, with just over 80% achieving undetectable PSA levels after treatment with PC-Spes (5). At a median follow-up of 16 months, no patient had any evidence of clinical or biochemical recurrence or progression. In the same study, they also found that 54% of patients with HRPC had a >50% decline in PSA with a median time to biochemical recurrence of 4 months. Similar findings were also reported by Oh *et al,* who reported a >50% decline in PSA in 52% of patients with HRPC (6). The reported effects of PC-Spes spread quickly among patient forums and although exact figures of its use were lacking, studies suggested that ~1-2 patients in 10 used alternative herbal medicine to treat their prostate cancer (7,8).

Concerns about PC-Spes were first raised in 2001 when patients noted rising PSAs despite continued treatment due to inconsistencies in the constituents of various batches. Concurrent case reports described an increased coaguability (9) and tendency to bleed (10) in patients on PC-Spes. An independent analysis of various samples at that time found a significant inter-batch variability of the proposed active ingredients as well as contamination with synthetic drugs including diethystilbesterol (DES) (equivalent to 0.5 mg/day), warfarin (equivalent to 1.5 mg/day) and indomethacin (equivalent to 30 mg/day) (11). Although the exact source of the contamination remained unclear, these findings highlighted the problem of consistency and reliability of herbal treatments. As a consequence, PC-Spes was withdrawn from the market in 2002.

The incidence of prostate cancer is on the increase, with >100,000 new cases and 35,000 deaths reported in the

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European Union alone per annum (12). At presentation, ~20% of patients had metastatic disease. While 80-90% initially responded to hormonal therapy, eventually all patients inevitably progressed to hormone refractory disease, which is usually fatal within 9-12 months (13). The relative paucity of effective therapies and the earlier promising effects of PC-Spes in HRPC have led to a renewed interest in its re-development.

Active Botanicals Ltd., a UK-based company has re-developed PC-Spes. Unlike the original, the new PC-Spes2 is standardized against 5 recognized active anti-neoplastic compounds (baicalin, oridonin, wogonin, isoliquiritigenin and Licochacone A) versus only 2 (baicalin and oridonin) in the old PC-Spes. All ingredients are sourced from a completely different processing plant in China to the original drug and the product is encapsulated within the UK. Random testing of PC-Spes2 samples from different batches and within each batch is performed with high pressure liquid chromatography (HPLC) to confirm consistent levels of the 5 active ingredients (Fig. 1). In addition, an independent analysis of random samples by the Laboratory of the Government Chemist (LCG Ltd.) UK using liquid chromatography/mass spectroscopy (LCMS) is performed to ensure no contamination with DES, indomethacin or warfarin occurs. The re-evaluation of PC-Spes2 *in vitro* and *in vivo* has confirmed the anti-neoplastic effect of this new compound (Table I).

Table I. The efficacy of PC-Spes 2 *in vitro*.[a]

Product and batch no.	LNCaP IC_{50} μg/ml	DU145 IC_{50} μg/ml
PC-Spes2 no. 0802-1	65	80
PC-Spes no. 5431106	106	159
PC-Spes no. 5431219	146	199

[a]PC-Spes2 is more effective than the old PC-Spes at inducing cell death in androgen-sensitive (LNCaP) and androgen-insensitive cells (DU145). The old PC-Spes shows considerable inter-batch variability.

The aim of this study was to evaluate the safety and efficacy of this new PC-Spes2 product in a single-centre, prospective, open pilot study in patients with advanced HRPC.

Patients and methods

The trial was undertaken at Frimley Park Hospital, Surrey (UK) with the approval of the local ethics committee. The study was carried out in line with the guidelines of good clinical practice and the declaration of Helsinki. A full verbal

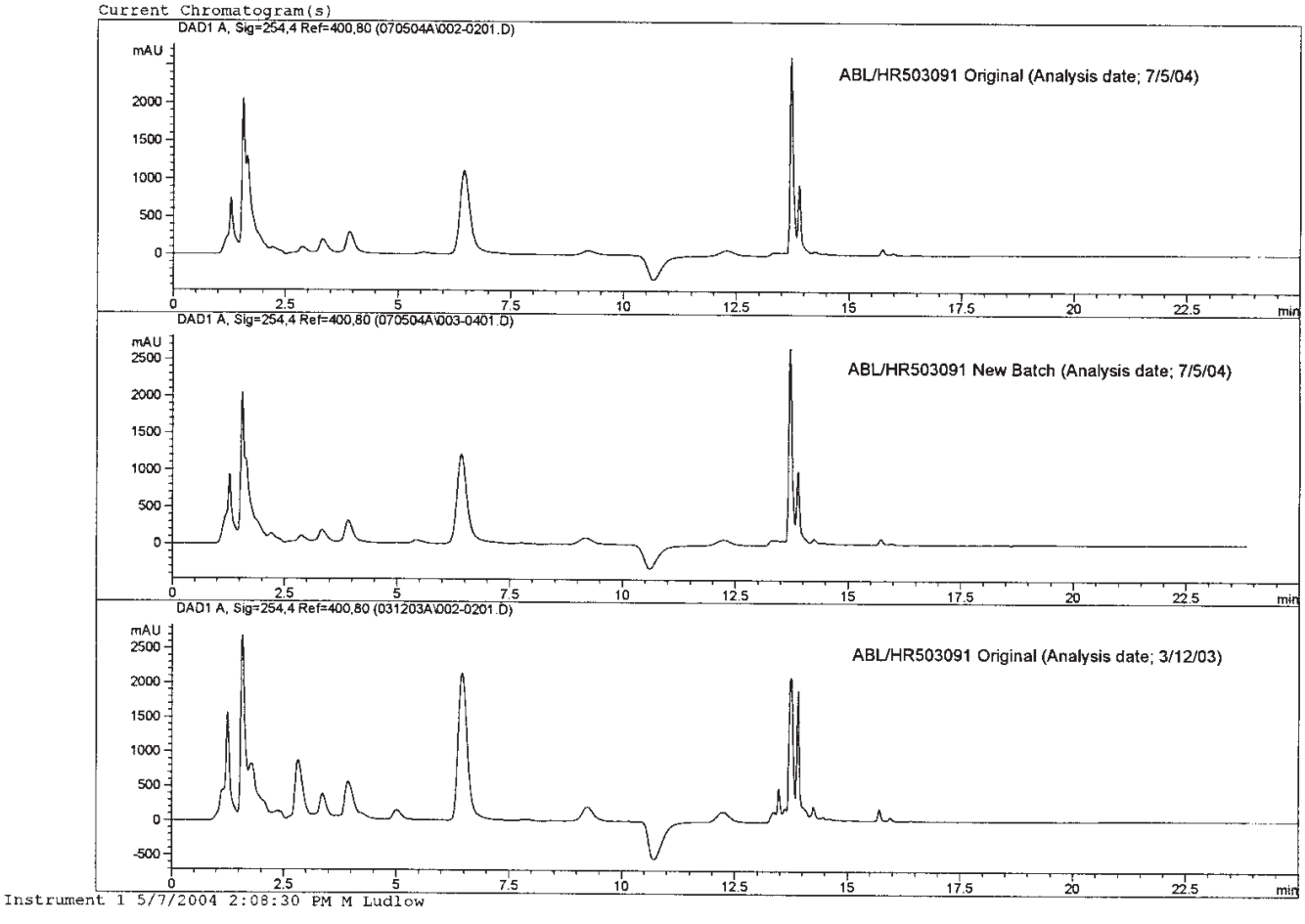

Figure 1. HPLC of different batches of PC-Spes2 showing a consistency of the active ingredients.

Table II. Patient characteristics.

	HRPC patients n=18
Age, years	
Median	72
Range	53-87
Presenting disease	
PSA median (ng/ml)	76.6
PSA range	4-532
Gleason grade	
Median	8
Range	4-9
Stage	
T2	5
T3	11
T4	2
Bone metastases at presentation	6/18
Previous local treatment	
EBRT	3
Bracytherapy	1
RRP	1
Previous systemic treatment	
Hormones + anti-androgen withdrawal	18
Chemotherapy	1
PSA at start of trial	
Median	110
Range	4-2870

and written explanation was provided to all patients prior to the study with written informed consent prior to participation.

Eligibility. All patients had histologically-proven prostate cancer. Hormone refractory status was confirmed by three successive rises in PSA measured >2 weeks apart, after second-line hormonal manipulation (i.e.: LH/RH analogue or orchidectomy and anti-androgen treatment and withdrawal). All patients had a life expectancy of >3 months and an ECOG performance status of 0-2.

Exclusion criteria included patients with a history of deep vein thrombosis, pulmonary embolism or a history of myocardial infarction within the past 5 years. Patients also excluded were those with <30 days from the instigation of other treatments including chemotherapy, Megace, steroids, anti-androgen withdrawal and radiotherapy. No patient had previously used the old PC-Spes or was currently on warfarin. Required biochemical parameters for all patients included haemoglobin >9x10^9/l, a white cell count >3x10^9/l, platelet count >120,000x10^9/l, normal liver function tests and cholesterol levels.

The pre-treatment evaluation included a history, physical examination, assessment of performance status and quality of life (QoL) assessment using the validated EORTC QLQ-C30 questionnaire. All patients had laboratory tests including PSA, a full blood count, urea and electrolytes, liver function tests, bone profiles, random blood sugar, clotting and triglyceride profiles. The post-treatment evaluation included a history and examination at 1, 3 and 6 months with laboratory assessment of PSA and clotting, as well as a re-assessment of QoL using the EORTC questionnaire. Patients were withdrawn if they developed significant toxicity or complications.

Treatment plan. Patients initially received 3x320 mg t.d.s. for the duration of the trial based on the dose of PC-Spes used in previous phase II trials (5). Those who subsequently found it difficult to tolerate this dose due to GI side effects were allowed, with the investigators' consent, to reduce their dose to 2x320 mg tablets t.d.s. An improved dosing regime was introduced to help combat the GI side effects, which involved patients receiving 1x320 mg tablets t.d.s. for 1 week, followed by 2x320 mg t.d.s. for 1 week and 3x320 mg t.d.s. for the duration of the trial. All patients were advised to take aspirin of 75 mg during the trial because of the previously described potential of thrombogenic risk of PC-Spes.

End points and statistical design. The primary end point of this study was to evaluate the safety and toxicity of PC-Spes2 in patients with advanced HRPC. The secondary end point was to assess the biochemical (PSA) response to treatment by assessing changes in the PSA doubling time (PSADT), PSA velocity (PSAV) and calculating the proportion of patients who achieved a ≥50% decline in PSA as an accepted means of assessing improved survival and outcome in patients with prostate cancer (14,15). In addition, the effect of treatment on patient QoL was also assessed. Differences in PSA were reported as means ±95% confidence intervals and the differences were compared using non-parametric tests.

Results

A total of 18 patients were enrolled into the trial between January 2004 to the present. The patient characteristics are outlined in Table II.

Only 3 out of 18 patients remained on the trial for 6 months. One patient died with advanced malignancy within 2 weeks of starting the trial, one patient was excluded from the study for repeated protocol violation with dosing and follow-up, one patient stopped the trial due to a rapidly rising PSA (>1000 in <3/12) and two patients left the trial despite a declining PSA to try alternative therapies. The remaining 10 out of 18 patients halted the trial due to moderate to severe diarrhoea. This affected 8 out of the first 10 patients enrolled in the study, who halted treatment at 1 month. Only 2 out of the last 8 patients enrolled halted the trial at 3 months due to troublesome diarrhoea. The reduction in GI upset was due to the improved dosing regime. No serious adverse events related to the treatment were observed. No thromboembolic events occurred and no changes in INR were detected in any of the patients during the study period. No patient had a decline in their QoL while on the trial, with a median improvement in QoL from 5 to 6 in patients still on the trial at 6 months.

Although no patient achieved a ≥50% reduction in PSA during the study period, of the 5 patients still on the trial at 3

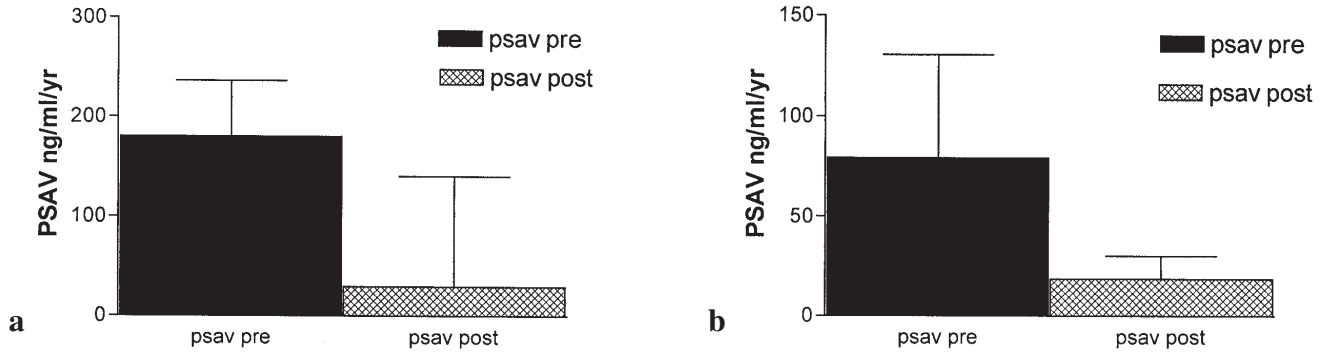

Figure 2. a, The change in PSAV at 3 months (p=0.22) and b, change in PSAV at 6 months (p=0.4).

months, 4 out of 5 (80%) showed an increase in PSADT and a decrease in PSAV [from 180.2 ng/ml/yr (95% CI: 24.2 to 336.2) to 29.40 ng/ml/yr (95% CI: -278.5 to 337.3)]. All 3 patients still on PC-Spes2 at 6 months (100%) showed an increase in PSADT and a decrease in PSAV [from 79.3 ng/ml/yr (95% CI: -141 to 299) to 18.7 ng/ml/yr (95% CI: -31.1 to 68.4)]. However, due to the small numbers, neither of these changes was statistically significant (p=0.22 and 0.4 for 3 months and 6 months PSAV respectively, Fig. 2a and b).

Discussion

Treatment options for advanced prostate cancer once it becomes hormone refractory are very limited. While newer chemotherapeutic regimes such as docetaxel have shown considerable promise, HRPC remains a fatal condition with a high level of morbidity. Despite their efficacy, drugs such as docetaxel have considerable common toxic side effects including severe fatigue, bone marrow suppression, hair loss, painful mouth ulcers and diarrhoea. The invasive nature of treatment and the inherent toxicity of such drugs can cause considerable distress and harm to terminal patients during treatment.

Alternative therapies for advanced cancer have always been attractive to patients and the cause of much skepticism among the medical community. Part of the problem is the lack of evidence-based medicine behind the numerous herbal therapies and concerns about the consistency of the proposed active ingredients. Unlike other herbal compounds, the original PC-Spes was shown to be effective in extensive laboratory based studies *in vitro* and *in vivo* with >40 research articles indexed on Medline (16). Its downfall came due to poor product consistency and unexplained contamination noted during clinical trials. Earlier skepticism regarding its efficacy being due to contamination with diethylstilbesterol (DES) has been resignedly refuted by studies which assessed the molecular effects of the two compounds. Uncontaminated PC-Spes altered the expression of 156 genes in prostate cancer cells after 24 h of exposure, compared to only 62 genes after treatment with DES. Only 6 genes were inhibited by both DES and PC-Spes (10%) (17).

PC-Spes2 is based on the same anti-neoplastic compounds as the old PC-Spes, but has the advantage of tightly-controlled, contamination-free production. The end result is a reliable, consistent and effective herbal compound. Independent testing showed no variability in the active ingredients within the same batch or between batches. Similarly, no contamination with DES, thromboembolic events or alterations in clotting parameters was noted, dispelling the fears of the earlier preparations.

This preliminary study had two main endpoints, looking at the safety and efficacy of PC-Spes2. While no patient had any serious adverse event, 10 out of 18 patients stopped the trial due to moderate to severe diarrhoea. The exact cause of this diarrhoea is unclear, although the subsequent altered dosing regime did improve the incidence of this side effect, with only 2 out of the last 8 enrolled patients developing diarrhoea vs. 8 out of the first 10 patients enrolled using the older dosing regime. As Pc-Spes2 is taken orally, severe GI upset may lead to an altered absorption of the drug and may explain the reduced efficacy versus the older PC-Spes, which had few problems with GI disturbances. This may explain why all patients who remained on the trial had a beneficial response to treatment, with marked increases in their PSADT and decreases in their PSAV, but failed to achieve a >50% decline in their PSA as previously described with PC-Spes. The small number of patients remaining on the trail at 6 months (3 out of 18) made statistical analysis difficult and no statistical significance was evident despite the magnitude of changes in PSAV (79.3 to 18.7 ng/ml/yr at 6 months).

One major difference between the old PC-Spes and the new compound is the proportion of the active components. The old compound was only standardized against 2 active ingredients (baicalin and oridonin) which constituted ~10% of the overall compound. PC-Spes2, on the other hand, is standardized against 5 active anti-neoplastic components (baicalin, oridonin, wogonin, isoliquiritigenin and Licochacone A), a total of ~80% of the overall compound. The greater concentration of flavonoids in the new preparation may be the cause of the increased diarrhoea, and, while the greater concentration of anti-neoplastic ingredients translated to greater efficacy *in vitro*, this did not translate to a better anti-cancer agent in the clinical trial due to the reduced tolerability and supposed reduced bioavailability. A further refinement of the active ingredients may be required to achieve an optimum anti-neoplastic action, while minimizing the systemic side effects before the ideal formulation is achieved.

In conclusion, for any herbal medication to become widely accepted into mainstream medical practice it has to withstand the same rigorous scrutiny of research as other hopeful drug

treatments. The first major hurdle of purity and standardization has been successfully achieved with this new preparation. However, while PC-Spes2 has been shown to be effective in laboratory studies, its effect in this prospective clinical trial has been disappointing compared to the responses widely described with the old PC-Spes. The refinement of the active ingredients to achieve an optimum anti-tumor action while reducing its GI side effects will be the following hurdle before considering further evaluation in clinical trials. Given the earlier responses of androgen-sensitive tumors to PC-Spes, the new formulation also warrants further evaluation in this subgroup as a potential means of treating prostate cancer without developing hormone refractory disease.

References

1. Halicka HD, Ardelt B, Juan G, *et al*: Apoptosis and cell cycle effects induced by extracts of the Chinese herbal preparation PC-SPES. Int J Oncol 11: 437-448, 1997
2. Tiwari RK, Geliebter J, Garikapaty VP, Yedavelli SP, Chen S and Mittelman A: Anti-tumor effects of PC-SPES, an herbal formulation in prostate cancer. Int J Oncol 14: 713-719, 1999.
3. de la Taille A, Buttyan R, Hayek O, *et al*: Herbal therapy PC-SPES: *in vitro* effects and evaluation of its efficacy in 69 patients with prostate cancer. J Urol 164: 1229-1234, 2000.
4. Kubota T, Hisatake J, Hisatake Y, *et al*: PC-SPES: A unique inhibitor of proliferation of prostate cancer cells *in vitro* and *in vivo*. Prostate 42: 163-171, 2000.
5. Small E, Frohlich M, Bok R, *et al*: Prospective trial of the herbal supplement PC-SPES in patients with progressive prostate cancer. J Clin Oncol 18: 3595-3603, 2000.
6. Oh WK, George DJ, Hackmann K, *et al*: Activity of the herbal combination, PC-SPES, in the treatment of patients with androgen-independent prostate cancer. Urology 57: 122-126, 2001.
7. Lippert MC, McClain R, Boyd JC and Theodorescu D: Alternative medicine use in patients prostate carcinoma treated with curative intent. Cancer 86: 2642-2648, 1999.
8. Kao GD and Devine P: Use of complimentary health practices by prostate carcinoma patients undergoing radiation therapy. Cancer 88: 615-619, 2000.
9. Lock M, Lublaw DA, Choo R and Imrie K: Disseminated intravascular coagulation and PC-SPES: a case report and literature review. Can J Urol 8: 1326-1329, 2001.
10. Weinrobe MC and Montgomery B: Acquired bleeding diathesis in a patient taking PC-SPES. N Engl J Med 345: 1213-1214, 2001.
11. Sovak M, Seligson AL, Konas M, Hajduch M, Dolezal M, Machala A and Nagourney R: J Natl Cancer Inst 94: 1275-1281, 2002.
12. Hamdy FC and Thomas BG: New therapeutic concepts in prostate cancer. BJU Int 88: 43-48, 2001.
13. Crawford ED, Rosenblum M, Ziadi AM and Lange PH: Overview: Hormone refractory prostate cancer. Urology 54: 1-7, 1999.
14. Bubley GJ, Carducci M, Dahut W, *et al*: Elgibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer. Recommendations from the PSA working group. J Clin Oncol 17: 3461-3467, 1999.
15. Lee AK, Levy LB, Cheung R and Kuban D: Prostate-specific antigen doubling time predicts clinical outcome and survival in prostate cancer patients treated with combined radiation and hormone therapy. Int J Radiat Oncol Biol Phys 63: 456-462, 2005.
16. White J: PC-SPES - a lesson for future dietary supplement research. J Natl Cancer Inst 94: 1261-1263, 2002.
17. Bonham M, Arnold H, Montgomery B, *et al*: Molecular effects of the herbal compound PC-SPES: Identification of activity pathways in prostate carcinoma. Cancer Res 62: 3920-3924, 2002.