Prostate Cancer and Prostatic Diseases (2003) 6, 301–304
 1365-7852/03 $25.00
www.nature.com/pcan

Modified citrus pectin (MCP) increases the prostate-specific antigen doubling time in men with prostate cancer: a phase II pilot study

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This trial investigated the tolerability and effect of modified citrus pectin (Pecta-Sol®) in 13 men with prostate cancer and biochemical prostate-specific antigen (PSA) failure after localized treatment, that is, radical prostatectomy, radiation, or cryosurgery. A total of 13 men were evaluated for tolerability and 10 for efficacy. Changes in the prostate-specific antigen doubling time (PSADT) of the 10 men were the primary end point in the study. We found that the PSADT increased (*P*-value < 0.05) in seven (70%) of 10 men after taking MCP for 12 months compared to before taking MCP. This study suggests that MCP may lengthen the PSADT in men with recurrent prostate cancer.
Prostate Cancer and Prostatic Diseases (2003) **6,** 301–304. doi:10.1038/sj.pcan.4500679

Keywords: prostate-specific antigen doubling time; modified citrus pectin; spline regression

Introduction

A nutrient of recent interest to cancer researchers is citrus pectin, a natural substance found in the peel and pulp of citrus fruits such as lemons, grapefruits, oranges, and tangerines. Citrus pectin is a complex polysaccharide with abundant galactosyl (sugar carbohydrate) residues. In the laboratory, citrus pectin is modified (MCP) by adjusting the pH to produce smaller and shorter chain molecules that are more easily absorbed in the intestinal tract for human consumption.[1]

Research indicates that cell–cell interactions are mediated by cell surface molecules called carbohydrate-binding proteins (CBP) or lectins. One such lectin, galectin-3, has been implicated in the metastatic process and appears to be expressed more by metastatic cells than by the primary tumor cells.[2,3] The correlations between the level of galectin expression and tumor stage have been documented for colorectal, gastric, and thyroid cancers. Antigalectin monoclonal antibodies have also been shown to inhibit the growth of tumor cells in culture.[4] It is hypothesized that these higher galectin levels permit greater adhesion and clumping of cancer cells at a 'target site,' that is, the site of metastasis. MCP appears to act as a ligand for the galectin-3 receptor sites, binding to galectin-3, and thereby blocking the ability of tumor cells to adhere to one another. This prevents the aggregation of tumor cells and their subsequent adhesion to target sites such as the endothelial cells.[5,6]

In 1995, Pienta *et al*[7] studied the effects of MCP on the rate of development of pulmonary metastases in a controlled trial in MAT-LyLu Dunning rats. The MAT-LyLu tumor is a poorly differentiated and rapidly growing subline of the Dunning R3327 rat prostate adenocarcinoma model of prostate cancer. The rats received either 0.1 or 1% MCP in drinking water or served as untreated controls. The results of the study showed that 15/16 (93.75%) of the control animals developed lung metastases in comparison to 7/14 (50%) of the 0.1% MCP-treated rats and 9/16 (56.3%) of the 1% MCP-treated rats. Moreover, 13% of the rats receiving 1% MCP were found to have lymph node metastases *vs* 55% of the control rats.[7]

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Received 1 May 2003; revised 3 July 2003; accepted 8 July 2003

In another *in vivo* study, MCP was demonstrated to inhibit mammary and colonic tumor growth and metastasis by inhibiting carbohydrate-mediated angiogenesis by blocking the association of galectin-3 to its receptors.[8]

Since galectin-3 has been shown to be present in the human prostate cancer cell line PC-3 and also detected in the human prostate cancer tissue, we carried out a phase II pilot study using MCP in 13 men with prostate cancer.

All men in the study were experiencing serial increases in PSA after localized treatment, that is, radical prostatectomy, radiation, or cryosurgery. The objective of the study was to determine the effectiveness of MCP at increasing the prostate-specific antigen doubling time (PSADT).

Patients and methods

The study protocol was approved by the Daniel Freeman Memorial Hospital Institutional Review Board for use in human subjects involved in medical research. All the study participants provided informed consent before enrollment in the study.

This was a nonrandomized phase II pilot study of MCP. Each patient in the study served as his own control since the rate of prostate-specific antigen (PSA) change or PSADT was being compared before and after the intervention. The patients were encouraged to make no significant changes in their diet, use of other nutritional supplements, or current prescription medications during the pre- and post-study period.

Patients selected for this study had biopsy-confirmed adenocarcinoma of the prostate, were untreated at the time of entry into the study, and had low but progressively rising PSA levels (<10 ng/ml). All the patients included in the study had biochemical PSA failure following an attempt at local curative therapy (eg radical prostatectomy, external beam radiation, or cryosurgery), and eight of the patients had previously been treated with androgen-deprivation therapy (ADT). Patients had at least three rising PSA levels documented prestudy over not less than a 6-month interval. Patients who had received prior ADT must have had a stable or steady-state serum testosterone level of ≥ 150 ng/ml for at least 6 months prior to being included in the study.

The evaluation of the participants began with a baseline physical examination by the physician, system review, and performance status assessment using the ECOG criteria. The system review, ECOG assessment, PSA, chemistry, and hepatic panels were repeated approximately every 4 weeks for the duration of the trial.

Each participant in the study received Pecta-Sol® (Econugenics Santa Rosa, CA) in 800 mg, powder-filled capsules. The total daily dosage of Pecta-Sol® in this study was 18 capsules per day (14.4 g) taken in three divided doses with eight ounces of water or juice. The patient tolerability of Pecta-Sol® was assessed by comparing the results of weekly self-assessment diaries with baseline assessments. No formal method of determining the patients' compliance with the prescribed amount of Pecta-Sol® was used. However, the investigators questioned the participants monthly about study compliance and it was thought to be excellent.

The primary end point of the study was the rate of change in PSA or the PSADT before and after the start of MCP. PSA measurements before and after the start of the treatment with MCP were taken frequently (monthly in most cases) in a single laboratory by the same technician. The PSA assay used was the Immulite I, third generation (Diagnostic Products Corp., Los Angeles, CA, USA), a completely automated, ultrasensitive chemiluminescence assay with a sensitivity limit of 0.003 ng/ml.

Research related to Prostate cancer in men indicates that PSA levels continue to increase without intervention. This increase in PSA follows a constant linear rate with time when expressed as log PSA.[9] The serum PSA levels have been shown to be a reliable surrogate marker of prostate cancer growth[10,11] and, therefore an increase of the PSADT should correlate with decreased tumor growth.

Statistical analysis

There are two common methods of calculating PSADT. Both use points of the form $(x, y) = (\text{time}, \log \text{PSA})$. The first method uses only the first and last point and the slope of the line connecting them. The second uses the slope of the line fitted to all the available points. In either case, the PSADT is the logarithm of 2 divided by the slope.

While the values obtained using these two methods are often similar, using all of the data is better and can produce estimates with much less variance than using just two data points. Since linear regression is more accurate and uses all the available data, it is the preferred method of calculating PSADT. However, when one is faced with calculating and then comparing the PSADT before and after the start of a certain therapy, some problems are encountered. One might fit two separate regression lines to compute pre- and post-treatment PSADTs, but then the fit will have a discontinuity at the start of therapy. Moreover, one is faced with the additional task of evaluating the significance of any observed difference in the two doubling times.

These problems can be overcome with a new method previously described by our group using a best-fitting spline.[12] The spline fit method of measuring and comparing PSADT before and after the start of therapy is simple, yet accurate. The method involves using a single regression analysis for all pre- and postdata to fit a broken line with the break at time t_0 of treatment initiation. This is illustrated using the PSA measurements before and after the start of MCP for patient number 9 in Table 1 (see Figure 1). The regression model for this is:

$$y = \alpha + \beta t + \gamma s(t) \qquad (1)$$

where $y = \log$ (PSA), t is the time, and $s(t) = \max(t - t_0, 0)$. Here, $s(t)$ is a basic linear spline with a knot at t_0.

This method overcomes the previously mentioned problems. It uses all the data, produces a fit that has no jump at the time of treatment initiation, and the significance of the difference in PSADTs is simply the significance of the estimate of γ. This may be read directly from the regression output.

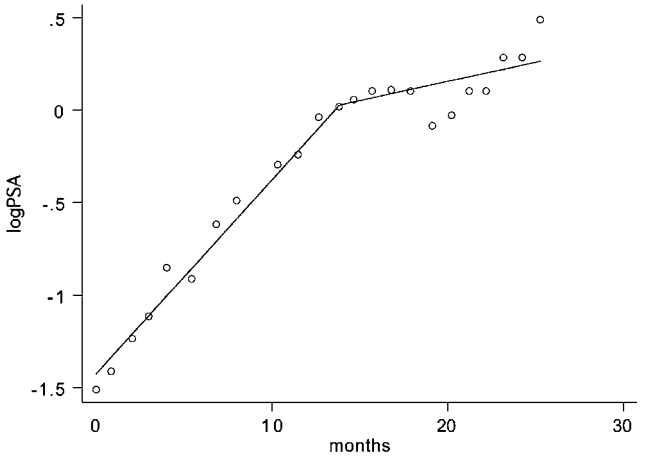

Figure 1 *Log-transformed PSA measurements y for patient number 9 before and after taking MCP plotted against time t in months and the fit of a linear spline with a break point at the time of treatment initiation ($t_0 = 13.67$ months) with MCP.*

Table 1 Patient age, prostate cancer characteristics prior to local therapy, previous treatment, and baseline PSA and testosterone

Pt. no.	Age	TNM tumor stage	Gleason score	Prestudy Treatment[a]	Pre-study PSA (ng/ml)	Prestudy baseline testosterone (ng/ml)
1	69	T2a	5	RP/IADT	0.519	471
2	79	T2b	7	RP/IADT	0.767	248
3	69	T1c	7	RP/RT/IADT	0.105	290
4	68	T2b	7	RT	4.2	474
5	78	T3c	7	CRYO/IADT	1.160	210
6	71	T2a	7	RP/RT/IADT	1.650	443
7	79	T3c	9	RP/RT/IADT	0.155	516
8	57	T2a	7	RP/IADT	0.209	313
9	62	T2a	7	RP	1.020	587
10	64	T2b	6	RT/IADT	0.520	337

[a]RP=radical prostatectomy, RT=radiation therapy, CRYO=cryotherapy, IADT=intermittent androgen-deprivation therapy.

Table 2 PSA doubling time before and after MCP

	PSA doubling time (months)			
Pt. no.	Pre-MCP	Post-MCP	Percent increase	*P*-value
1	3.97	13.43	238	<0.0001
2	1.12	2.83	152.5	0.0014
3	3.3	7.66	132	0.0002
4	30.82	54.93	78	0.2352
5	10.49	7.96	−24	0.8279
6	3.64	3.28	−10	0.5667
7	1.96	5.56	183.6	0.0004
8	2.33	3.24	38.9	0.01
9	6.596	33.3	404.8	<0.0001
10	5.18	50.13	867.7	0.00065

Results

A total of 13 patients were enrolled in the study, of which 10 were evaluable for efficacy. Table 1 lists the patient characteristics for the 10 evaluable patients. Table 2 lists the response of PSADT to MCP. Eight (80%) of the 10 patients had an increase in PSADT post-study in comparison to prestudy. However, only seven (70%) of the 10 were statistically significant (P-value ≤ 0.05). No patient had a decrease in absolute PSA.

MCP was well tolerated by all 10 of the evaluable patients. Three patients (23%) withdrew from the study due to side effects (two with mild abdominal cramps, one with mild diarrhea) that resolved soon after stopping the MCP. There were no serious side effects in any patient.

Discussion

The primary end point of our study was the change, if any, in the PSADT of men with prostate cancer before and after taking MCP. A statistically significant increase in PSADT was observed in seven of the 10 evaluable cases in which each patient acted as his own control. Intuitively, it seems that increasing the time it takes for the PSA level to double, if sustained, would mean that cancer progression would be slower and could conceivably result in a prolongation of life.

The clinical usefulness of PSADT to predict disease progression in men with prostate cancer has been reported in multiple studies. In a widely cited paper by Pound *et al*,[13] a PSADT of less than or equal to 10 months in men with biochemical PSA recurrence after radical prostatectomy was predictive of the probability and time to the development of metastatic disease. Roberts *et al*,[14] found that patients with a PSADT of less than 6 months had a 5-y freedom from systemic progression (SP) of only 64%. In contrast, they found that the 5-y freedom from SP with a PSADT of longer than 1 y was 95%. A short PSADT after definitive radiotherapy also predicts more rapid progression to symptoms.[15–17] The PSADT in men under observation alone has been shown to be the most powerful indicator of disease activity.[18]

Although the use of PSADT to help predict those patients who will develop clinically progressive disease has been well established; it has not been established whether therapeutically altering or increasing the doubling time will impact the measurable clinical end points such as the development of metastatic disease or prolonged survival.

Favorable changes in PSADT may have research implications beyond its potential impact on the cancer-specific survival. Evaluating the changes in PSADT in response to therapy may be an efficient *in vivo* method for screening nontoxic agents. It is conceivable that marginally effective agents (those that increase the PSADT, but do not cause a decline in PSA) might become clinically valuable when used in combination with other anticancer agents.

Two previous studies of 1,25-dihydroxyvitamin D_3 (calcitriol) illustrate this idea. The first study looked at the effect of calcitriol given daily at slowing the rate of PSA rise compared to the pretreatment rate in seven men with early recurrent prostate cancer. The study found a

significant increase in the PSADT in six of seven patients during *vs* before calcitriol therapy.[19] The second study evaluated weekly pulse (high dose) calcitriol in 22 men with recurrent prostate cancer. Three patients had confirmed reductions in PSA and three additional patients had a significant increase in their PSADT.[20]

On the basis of these results, studies of high-dose pulse calcitriol in combination with docetaxel (Taxotere®) have been carried out and have shown notable synergy with more frequent and deeper PSA declines in men with advanced prostate cancer compared with single-agent docetaxel.[21]

Obviously, changes in PSADT after intervention with agents such as MCP have to be interpreted with caution. As we are not directly measuring tumor volume, we do not know whether these changes are a result of the death of cancer cells or some other PSA-altering mechanism. While our study period of 12 months was adequate to assess the effect of MCP on PSADT, clearly this short period of time was not adequate to evaluate the long-term effect of changes in PSADT on prostate cancer-related survival.

Conclusions

In this study, we attempted to determine the effect of a nutritional supplement MCP (Pecta-Sol®) on the rate of PSA increase or PSADT in 10 men with biochemical PSA failure after definitive local therapy for prostate cancer. We observed that seven (70%) of the 10 patients had a statistically significant (P-value <0.05) increase in PSADT after taking MCP for 12 months, in comparison to before taking MCP.

The long-term impact that MCP will have on disease progression is unknown. More research is still necessary to define the role of MCP fully in prostate cancer treatment.

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