Nutrition and Cancer

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/hnuc20

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Published online: 27 Jan 2010.

To cite this article: Tony Choon Seng Woo, Richard Choo, Mary Jamieson, Sarat Chander & Reinhold Vieth (2005) Pilot Study: Potential Role of Vitamin D (Cholecalciferol) in Patients With PSA Relapse After Definitive Therapy, Nutrition and Cancer, 51:1, 32-36, DOI: 10.1207/s15327914nc5101_5

To link to this article: http://dx.doi.org/10.1207/s15327914nc5101_5

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Pilot Study: Potential Role of Vitamin D (Cholecalciferol) in Patients With PSA Relapse After Definitive Therapy

Tony Choon Seng Woo, Richard Choo, Mary Jamieson, Sarat Chander, and Reinhold Vieth

Abstract: When local treatments for prostate cancer have failed, and prostate-specific antigen (PSA) rises in the absence of symptoms, there is little consensus as to the best management strategy. Calcitriol has been shown to prolong the doubling time of PSA in this context, but near-toxic doses are required. We investigated the effect of the nutrient vitamin D (cholecalciferol), a biochemical precursor of calcitriol, on PSA levels and the rate of rise of PSA in these patients. Fifteen patients were given 2,000 IU (50 µg) of cholecalciferol daily and monitored prospectively every 2–3 mo. In 9 patients, PSA levels decreased or remained unchanged after the commencement of cholecalciferol. This was sustained for as long as 21 mo. Also, there was a statistically significant decrease in the rate of PSA rise after administration of cholecalciferol (P = 0.005) compared with that before cholecalciferol. The median PSA doubling time increased from 14.3 mo prior to commencing cholecalciferol to 25 mo after commencing cholecalciferol. Fourteen of 15 patients had a prolongation of PSA doubling time after commencing cholecalciferol. There were no side effects reported by any patient. Further study is needed to confirm this finding and to explore the potential therapeutic benefit of nutrient vitamin D in prostate cancer.

Introduction

A common problem encountered by the clinician treating prostate cancer is the patient who has a rising serum prostate-specific antigen (PSA) level, while not having any symptoms or signs of relapse. The optimal management of such a patient is not well defined. Although androgen ablation is traditionally the next line of management, the optimal time to introduce these drugs for progressively rising but minimally elevated PSA levels remains unknown, as there is no randomized study suggesting any survival benefit of immediate androgen ablation in this clinical setting. Androgen ablation has a finite duration of efficacy and has potentially serious side effects. Thus, many clinicians opt for active surveillance alone in this clinical situation. On the other hand, it is distressing to the patient to remain idle in the presence of steadily rising PSA. Under this circumstance, it would be of great benefit to patients if there were an effective agent with low toxicity that inhibited or decreased the rate of tumor progression before consideration of androgen ablation. With this goal in mind, we investigated the potential therapeutic effect of a much less toxic agent, nutrient vitamin D (cholecalciferol) in patients with isolated PSA relapse.

Preclinical laboratory findings suggest that 1,25-dihydroxyvitamin D (calcitriol) retards prostate cell growth in vitro. When nutritional vitamin D (cholecalciferol) is ingested, it is hydroxylated in the liver into 25-hydroxycholecalciferol and then hydroxylated again by the kidneys to become the active hormone, calcitriol. Normal prostate cells also synthesize calcitriol from 25-hydroxycholecalciferol (1,2). Prostate cancer cells have a diminished capacity for hydroxylation of 25-hydroxycholecalciferol; however, these cells could possibly still be affected by calcitriol that is synthesized by neighboring cells or produced in the kidneys (2). Prostate cancer cells respond to calcitriol by slowing their rate of replication (1,3). Vitamin D metabolites have been shown to increase differentiation and apoptosis, and decrease proliferation, invasiveness, and metastasis of prostate cancer cells (4). The concentrations of calcitriol required to cause this response in prostate cancer cells are well in excess of those seen in normal physiology. However, physiologic concentrations of 25-hydroxycholecalciferol (a metabolite of cholecalciferol) can also produce this response (1,4). One recent report showed that physiologic concentrations of 25-hydroxycholecalciferol could affect prostate cells through a mechanism that did not appear to involve calcitriol (5). Taken together, the laboratory studies suggest that nutritional cholecalciferol supplementation to increase 25-hydroxycholecalciferol may have effects of the same magnitude on prostate cancer cells as calcitriol.

Two clinical studies have been published on the effect of calcitriol in humans. Gross et al. treated seven patients with rising PSAs after radiation or prostatectomy with 0.5–2.5 µg
calcitriol daily (6). The rate of PSA rise decreased in six of the seven patients, but development of hypercalcuria limited the dose of calcitriol that could be given. Beer et al. treated 22 patients with a large, once-weekly dose of 0.5 µg/kg and reported a slower rate of rise in PSA (7). This trial included patients with a range of different prostate cancers, with four patients having cancer with a Gleason score greater than 7. Although this high-dose protocol did not cause hypercalcemia, it was necessary for patients to restrict their calcium intakes significantly.

To date, vitamin D, an inexpensive nutritional supplement, has not been studied as an agent that might affect the rate of rise in PSA. The general public can safely ingest up to 2,000 IU (8,9) of vitamin D. This would increase 25-hydroxycholecalciferol levels by approximately 20 ng/dL (50 nmol/L; 10). This dose has been reported to improve bone pain scores and muscle strength in patients with metastatic prostate cancer (11). The aim of our pilot study was to observe the effect of nutritional vitamin D3 (cholecalciferol) on patients with prostate cancer (11). The aim of our pilot study was to observe the effect of nutritional vitamin D3 (cholecalciferol) on the rate of rise of PSA, PSA doubling times, and absolute PSA levels in biochemically relapsed prostate cancer. We tested the hypothesis that vitamin D supplementation might slow the rate of PSA rise in a similar manner to that which has been reported for calcitriol (6,7).

Materials and Methods

Eligibility

The work reported here was approved by the Review Ethics Board of the Toronto-Sunnybrook Regional Cancer Centre. All patients enrolled had histologically documented prostate cancer and had completed definitive local treatments (radical prostatectomy, radiotherapy with curative intent, or both). Patients had to have at least three successive rises in PSA over a minimum of 9 mo on serial measurements after their primary treatment and be free of symptoms of prostate cancer. Patients had to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 and no prior history of hypercalcemia, heart failure, acute myocardial infarction, or renal stones within the previous 6 mo. None had clinical or radiological evidence of distant metastasis.

Patients were given 50 µg (2,000 IU) per day of oral vitamin D3, which they could purchase over the counter without prescription (two 1,000 IU tablets of cholecalciferol per day). Patients were permitted to continue to take their usual medications and maintain their usual diets. Follow-up was every 2–3 mo and PSA was measured at each visit. Calcium levels were taken on all patients while they were on cholecalciferol at least 1 mo after commencement of cholecalciferol therapy.

Calculations and Statistical Methods

It was postulated that, without any intervention, the rate of rise of PSA and PSA doubling time would remain constant. To test this hypothesis, the five PSA readings taken prior to commencing cholecalciferol were divided arbitrarily into two time periods. An “early-pre” period comprised the fifth-last, fourth-last, and third-last PSA readings taken prior to commencing cholecalciferol. A “late-pre” period comprised the third-last, second-last, and last PSA readings prior to commencing cholecalciferol. Within each period, the slope of the natural logarithm of PSA vs. days time was calculated using the linear-regression slope function of Microsoft Excel (Redmond, WA).

These slopes were then expressed in terms of percent change in PSA per month and doubling time using the formulae:

\[ \text{% PSA change/month} = \left( \frac{\text{EXP} \times \text{LnPSA slope}}{365} \right) - 1 \times 100 \]

\[ \text{PSA Doubling Time} = \log(2)/\log(1 + P/100) \]

where \( P = \text{% PSA change/month} \); \( \text{EXP} = e \) raised to power.

For statistical testing, the percent change in PSA per month between the two periods prior to commencing vitamin D were compared with each other using a Wilcoxon rank sum test for paired data, using SPSS 11 software (Chicago, IL). Similarly, the percent change in PSA per month just prior to commencing vitamin D was compared with that after commencing vitamin D. Statistical testing was conducted on the percent change in PSA per month rather than on the PSA doubling time. This was because of difficulties with expressing PSA doubling along the same numerical continuum as PSA halving.

Results

Fifteen patients were enrolled. The mean length of time from definitive surgery or radiation to the commencement of cholecalciferol was 65 mo. The median follow-up from the start of cholecalciferol treatment was 8 mo (range, 4–21 mo). Table 1 shows the patient characteristics and types of treatments that were used before commencing cholecalciferol.

Changes in Absolute PSA Values

Of the 15 patients, 8 had a decrease in absolute serum PSA levels after commencing cholecalciferol. The decrease in PSA was sustained from 5 to 17 mo. In a ninth patient, PSA levels fluctuated around the baseline value for 21 mo and did not have any clear trend of increase at the time of last follow-up (Table 2).

Changes in PSA Doubling Time

In the absence of cholecalciferol supplementation, there was no significant change in the rate of rise of PSA (Fig. 1). There was no difference in the rate of rise in PSA between the two arbitrary time periods before commencing cholecalciferol treatment.
ferol \((P = 0.460)\). However, the rate of rise in PSA was significantly less after commencing cholecalciferol than just before commencing cholecalciferol \((P = 0.005)\). The PSA doubling time increased from a median of 14.3 months (range: 5.5 to 237) prior to commencing cholecalciferol to 25 months (range: doubling time of 8.9 mo to a halving time of 25 mo) after cholecalciferol supplementation. The PSA doubling time increased in 14 out of 15 patients.

**Side Effects**

Calcium levels remained normal in 14 of 15 patients after commencing cholecalciferol. One patient was found to have an elevated serum calcium level of 2.88 mmol/L (normal = 2.20–2.60 mmol/L) after commencing cholecalciferol and was subsequently diagnosed with a functioning parathyroid adenoma with hypersecretion of parathyroid hormone. There were no adverse effects reported by any patient.

**Discussion**

Our study supports the findings of two previous reports that vitamin D-based compounds can increase the doubling time in PSA in asymptomatic prostate cancer patients who have isolated PSA rise (6,7). The most striking aspect of the present work is that this effect occurred with a dose of vitamin D that has been stated by regulatory bodies as being safe for general public consumption (8,9). To put this dose into context, a healthy man can typically acquire 2,000 IU vitamin D/day through casual exposure to sunshine (12). The ingestion of this same dose as a tablet would essentially double the vitamin D supply of these patients.

The previous studies on humans used calcitriol rather than the nutrient form of vitamin D (6,7). These earlier studies were based on preliminary evidence showing that superphysiologic concentrations of calcitriol were needed to slow proliferation of prostate cells in culture and in mouse

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**Table 1. Clinical Characteristics of Each Patient Enrolled\(^a\)**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Clinical Stage</th>
<th>Grade</th>
<th>Primary Treatment</th>
<th>Time Since Primary Treatment (mo)</th>
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<tr>
<td>1</td>
<td>T2C</td>
<td>7</td>
<td>RT</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>T1C</td>
<td>6</td>
<td>RT</td>
<td>43</td>
</tr>
<tr>
<td>3</td>
<td>T2C</td>
<td>6</td>
<td>RT, then orchidectomy</td>
<td>76</td>
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<tr>
<td>4</td>
<td>T2C</td>
<td>6</td>
<td>RT</td>
<td>58</td>
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<tr>
<td>6</td>
<td>T2A</td>
<td>7</td>
<td>RP+PLND, then RT</td>
<td>29</td>
</tr>
<tr>
<td>7</td>
<td>T2A</td>
<td>5</td>
<td>NAA then RP, then RT</td>
<td>75</td>
</tr>
<tr>
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<td>T2C</td>
<td>9</td>
<td>RP, then RT</td>
<td>74</td>
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<tr>
<td>9</td>
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<tr>
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<td>7</td>
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<td>63</td>
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<tr>
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<td>T2B</td>
<td>7</td>
<td>RT</td>
<td>66</td>
</tr>
</tbody>
</table>

\(^a\) Abbreviations are as follows: RT, radiotherapy with curative intent; NAA, neoadjuvant androgen ablation; RP, radical prostatectomy; PLND, pelvic lymph node dissection.

**Table 2. Prostate-Specific Antigen (PSA) Profile of Each Patient**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>PSA Before Vitamin D (µg/l)</th>
<th>Lowest PSA after Vitamin D (µg/l)</th>
<th>Time to Nadir (mo)</th>
<th>Follow-Up on Vitamin D (mo)</th>
<th>Final PSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.9</td>
<td>1.65(^a)</td>
<td>9</td>
<td>13</td>
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<tr>
<td>2</td>
<td>4.43</td>
<td>3.93(^a)</td>
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<td>17</td>
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<tr>
<td>3</td>
<td>1.43</td>
<td>1.48</td>
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<td>2.71</td>
<td>1</td>
<td>12</td>
<td>3.32</td>
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<tr>
<td>5</td>
<td>4.97</td>
<td>4.05(^a)</td>
<td>5</td>
<td>13</td>
<td>6.3</td>
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<tr>
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<td>3.16</td>
<td>1.62(^a)</td>
<td>9</td>
<td>21</td>
<td>1</td>
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<tr>
<td>7</td>
<td>0.95</td>
<td>0.95</td>
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<tr>
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<td>1.06</td>
<td>1.34</td>
<td>1.5</td>
<td>6</td>
<td>1.66</td>
</tr>
<tr>
<td>9</td>
<td>1.71</td>
<td>1.6(^a)</td>
<td>2</td>
<td>8</td>
<td>1.15</td>
</tr>
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<td>10</td>
<td>0.58</td>
<td>0.52(^a)</td>
<td>9</td>
<td>9</td>
<td>0.38</td>
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<tr>
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<td>0.40</td>
<td>0.38(^a)</td>
<td>4</td>
<td>3.45</td>
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</tr>
<tr>
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<td>2.72</td>
<td>2.82</td>
<td>6</td>
<td>0.57</td>
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<tr>
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<td>0.44</td>
<td>0.45</td>
<td>4</td>
<td>1.75</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>1.47</td>
<td>1.75</td>
<td>5</td>
<td>5</td>
<td>9.45</td>
</tr>
</tbody>
</table>

\(^a\) Indicates a fall in absolute PSA level since starting Vitamin D.
models (13,14). More recent laboratory studies comparing the effects of 25-hydroxycholecalciferol with calcitriol in cultured prostate cells demonstrated that physiologic concentrations of 25-hydroxyvitamin D had the same effect as concentrations of calcitriol that are 100-fold higher than physiological concentrations (1,4,15,16). A study by Lou et al. using human prostatic stromal cells showed that, at physiological concentrations, 25-hydroxyvitamin D does not have to be converted to calcitriol to induce target-gene expression, suppress cell growth and induce expression of the activating enzyme, 1-alpha-hydroxylase (16). The logical implication of this latter research is that future studies looking at the effect of vitamin D analogs in prostate cancer should focus on the nutrient form of vitamin D (cholecalciferol), which effectively increases circulating 25(OH)D levels, rather than the hormone, calcitriol.

Clinicians have been increasingly faced with a management dilemma in patients with progressively rising, but minimally elevated PSA after definitive therapy. In the early stages of PSA relapse, there are concerns about administering androgen suppression drugs. In spite of the potential for serious side effects such as impotence, anemia, loss of muscle mass, and osteoporosis, there remains no randomized evidence suggesting that up front implementation of androgen ablation for PSA relapse alone improves quantity or quality of life, compared with delayed application at the time of evidence of tumor progression. Even without any treatment, patients may remain symptom-free for a long period of time. Partin et al. reported in a recent update of the Johns Hopkins Hospital experience that, in the absence of any intervention, median time from the onset of PSA relapse to the development of distant metastasis was about 7.5 yr in postsurgery patients and that median time from the development of distant metastasis to death was 6.5 yr (17). Under such a circumstance, a cheap agent with relatively few side effects, such as nutrient vitamin D, might be useful if it were able to prolong PSA doubling times.

It is unlikely that the results of this pilot study were due to chance. To decrease the likelihood of a false-positive result, patients were enrolled only if they had at least three consecutive PSA rises, which according to a consensus of experts from the American Society for Therapeutic Radiology and Oncology should eliminate most false cases of biochemical failure secondary to random fluctuations in PSA, or so-called “bounce” (18). Before intervention with cholecalciferol, the rate of rise of PSA was found in our study to be relatively constant. With cholecalciferol, PSA values fell or were stabilized for as long as 21 mo of follow-up in 9 of 16 patients. In these patients, it was possible to delay the implementation of androgen ablation.

Our study suggested that vitamin D may be effective in moderating the rate of PSA increase in these patients. Recently, a notion of “the rate of PSA increase” or “PSA doubling time” has become increasingly important in considering the underlying biological activity of malignancy and the likelihood of clinical manifestation of tumor progression (19). Partin et al. reported, in evaluating the natural history of prostate cancer progression after PSA relapse following surgery, that significant predictive factors for clinical manifestation of distant metastasis were PSA doubling time, relapse within 2 yr of surgery, and Gleason score (17). In their series, the risk of developing distant metastasis at 5 yr was 65% to 75% when PSA doubling time was less than 10 mo compared with 10–20% when PSA doubling time was greater than 10 mo. Thus, agents that lengthen PSA doubling time or decrease the rate of PSA increase might still be clinically useful, even if they did not reduce absolute PSA levels.

This was a pilot study. As such, there were several limitations. First, the sample size of our cohort was small, increasing the risk of a false-positive finding. Second, the follow-up of this study was very short. The potential long-term side effects of prolonged intake of moderate amounts of vitamin D are not well documented, although this is a nutrient that is absorbed routinely in nature through sunlight exposure. Third, there were no data on serum vitamin D levels, urine calcium, or parathyroid hormone before and after the commencement of vitamin D. Thus, it was difficult to quantify the effect of nutrient vitamin D supplementation on these parameters. Fourth, the dose of vitamin D in this study was arbitrarily chosen. Further study is needed to examine such issues as dose-response relationship. Finally, there was no control group. The previously published pilot studies that looked at the use of calcitriol in biochemically relapsed prostate cancer unfortunately also suffered from small sample size and lack of controls (6, 7). This is the first pilot study that investigated the use of nutrient vitamin D, rather than the more toxic compound calcitriol. Despite these shortcomings, the findings in this study are compelling enough to warrant a more rigorous clinical trial to examine a potential role for nutrient vitamin D.

Figure 1. Effect of cholecalciferol on rate of rise of PSA. Median and quartiles of rate of PSA increase prior to starting cholecalciferol (visits –4 to –2 and visits –2 to 0) and after starting cholecalciferol (visits 0 onward).
D in patients with isolated PSA relapse. In the doses that were given in this study, the agent is relatively free of side effects. As cholecalciferol is a nonproprietary molecule, the cost of the treatment used here was only $2.00 Canadian per month.

**Conclusion**

This pilot study suggests that a simple nutrient, vitamin D, may provide a therapeutic gain for patients with PSA relapse after definitive therapies, as it may be able to moderate the rate of PSA increase without any adverse side effects for the patient. As this is a pilot study, further work is needed to confirm these preliminary findings in the context of a larger randomized trial.

**Acknowledgments and Notes**

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Submitted 19 July 2004; accepted in final form 3 November 2004.

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