Vitamin D_3 (Cholecalciferol) in the Treatment of Biochemically-Relapsed Prostate Cancer

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Abstract

Purpose: When local treatments for prostate cancer have failed, and PSA rises in the absence of symptoms, there is little consensus as to the best management strategy. Calcitriol has been used to slow the rate of rise in PSA in this context, but near-toxic doses are required. We investigated the effect of the simple nutrient cholecalciferol, a biochemical precursor of calctriol upon PSA levels, and rate of rise of PSA.

Materials and Methods: 10 patients were given 2000IU (50 mcg) of cholecalciferol daily, and monitored prospectively every 2 months, recording PSA and toxicity symptoms.

Results: In 7 of 10 patients, PSA levels declined or remained unchanged for as long as 15 months. The rate of rise of PSA did not change before the intervention, but during cholecalciferol supplementation, the rate of rise of PSA decreased in 8 of 10 patients (p=0.028).

Conclusions: This preliminary study suggests that cholecalciferol can moderate the rate of rise in PSA, which in turn can delay the need to implement hormonal manipulation. The role of cholecalciferol in the prevention and treatment of prostate cancer deserves more rigorous study.

Introduction

When prostate cancer patients experience progressively rising PSA levels after having completed definitive therapies, androgen ablation is usually considered as the next line of treatment. However, the optimal timing of initiating hormonal therapies for isolated PSA relapse remains unknown, and there are no randomised studies suggesting a survival benefit of immediate androgen ablation in this setting. Also, this strategy only has a finite period of efficacy and frequent side effects. The clinician is faced with the dilemma of a patient who is distressed because of rising serum PSA, but who has no physical signs of being physically worse. There is some evidence to suggest that Vitamin D analogues can slow the rise of PSA in this setting. The aim of this study is to observe the effect of Vitamin D3 (cholecalciferol) upon the rate of rise of PSA, and absolute PSA levels in biochemically-relapsed prostate cancer.

METHODS

The work reported here was approved by the ethics review panel 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 3 successive rises in PSA over a minimum of 9 months on serial measurements after their primary treatment, and be asymptomatic. Patients had to have an 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 months. Patients with radiologically detectable bone or other metastases were excluded.

Patients were given 50mcg (2000IU) per day of oral cholecalciferol, a dose equal to the safe upper limit for this nutrient[1]. They were told not to alter their usual diet in any way. They were followed up 2-3 monthly and at each visit PSA and toxicity were recorded.

Calculations and Statistical Methods
Rate of Rise of PSA

The rate of rise of PSA was analysed for each patient using the following method. The linear regression slope of log PSA with time was calculated using Microsoft Excel (Redmond, WA). This method has been used by previous investigators[2]. This slope was then converted into units of perc

ent change per month, and doubling time. For example, a slope of $0.014X10^{-3}$ per day = an increase in PSA of 5% per month = a doubling time of 14 months.
It was postulated that without any intervention, PSA would rise at a constant rate. To test this hypothesis, the 5 PSA readings taken prior to commencing cholecalciferol were divided arbitrarily into 2 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. A third period comprised all PSA readings taken after the commencement of cholecalciferol. Statistical comparisons of the rate of rise in PSA between these 3 periods were done using the Wilcoxian rank-sum test, using SPSS 11 software (Chicago, IL).

RESULTS

10 patients were enrolled. The mean length of time from definitive surgery or radiation to the commencement of cholecalciferol was 63 months. The median follow-up from the start of cholecalciferol treatment was 9.3 months (range 3 - 15 months). Table 1 shows the patient characteristics and types of treatments that were used before commencing cholecalciferol.

Changes in Absolute PSA values

Of the 10 patients, 6 patients had a decrease in serum PSA levels after commencing cholecalciferol. The decrease in PSA was sustained from one to nine months. In a seventh patient, PSA levels fluctuated around the baseline value for 15 months and did not have any clear trend of increase at the time of last follow-up (Table 2).

Changes in Rate of Rise of PSA

In the absence of cholecalciferol supplementation, there was no significant change in the rate of rise in PSA (Figure 1). There was no difference in the rate of rise of PSA between the two arbitrary time periods before commencing cholecalciferol (p=0·959). However, the rate of rise of PSA was significantly less after commencing cholecalciferol than when compared with either of the pre-cholecalciferol timeframes (p=0·028 compared to the 3 "late-pre" visits just before starting cholecalciferol; p=0.047 compared to the 3 "early-pre" visits). The rate of rise of PSA dropped from a median of 4·5% (range: 0·3 to 13·5%) prior to commencing cholecalciferol to 1·6% per month (range: -14·7% to 6·6%) during cholecalciferol supplementation. The rate of rise of PSA decreased in eight of ten patients. There were no adverse effects reported by any patient.

DISCUSSION

Laboratory studies show that cholecalciferol metabolites and their analogues retard prostate cancer cellular adhesion, migration and growth [3]. Calcitriol analogues administered to rats with transplanted prostate tumors result in a decrease in size and weight of primary tumors and reduction in the number of metastases [4,5]. In prostate cancer patients, Gross et al reported on 7 patients who had a rise in PSA after definitive surgical or radiotherapy treatment for prostate cancer[2]. The patients were given up to 2.5mcg of calcitriol per day, resulting in a decrease in the rate of rise of PSA in 6 of the 7 patients. Beer et al. used a weekly high dose of calcitriol in 22 hormone-naïve patients with rising serum PSA after definitive local therapies. They found that PSA doubling times increased in 3 out of 22 patients, and a further 3 patients experienced a reduction in PSA levels after commencement of calcitriol[6]. Both clinical studies have been hampered by the use of calcitriol which causes hypercalcemia at the doses shown to have an effect upon prostate cancer in the laboratory. The approach we are reporting here was based on the recently evolving concept that, given appropriate supplies of calcidiol, the prostate can synthesize its own calcitriol in amounts that can be clinically relevant [7,8]. The liver readily converts cholecalciferol into calcidiol[9]. Prostate cancer cells metabolize calcidiol into calcitriol which acts in an autocrine manner to regulate proliferation and differentiation[10].
The cost of the treatment used here was Can. $2.00/month, and the dose is widely accepted as safe [1,9,11,12]. What must ultimately be proven is that the approach improves symptoms, local control or survival. We point out that almost no agent given to prostate cancer patients at the time of their first aymptomatic PSA rise has been proven to have any effect on these important clinical parameters.

The effects on PSA seen in this preliminary study compare favourably with results of earlier studies using calcitriol [13,14]. We enrolled patients with a history of at least 3 consecutive PSA rises, which according to a consensus of experts, should eliminate most false cases of biochemical failure secondary to random fluctuations in PSA, or so-called "bounce"[15]. Before intervention with cholecalciferol, PSA values continued to increase at a constant rate. With cholecalciferol, PSA values fell or were stabilized for as long as 15 months of follow-up. It is unlikely that any clinician would commence hormonal deprivation therapies when presented with an asymptomatic patient with a falling PSA. In more than half of our patients, hormonal therapy could have been delayed when cholecalciferol was commenced.

CONCLUSION

This was a pilot study with positive results that must be confirmed. Future research must address dose levels of cholecalciferol, measure serum levels of calcidiol, calcitriol, and calcium in patients who have isolated PSA recurrence. Although the level of cholecalciferol which was given here could be described as being a high physiological dose, unlikely to be harmful to most patients, it remains controversial whether this agent is of net benefit [16,17]. Therefore, our recommendation is for the use of cholecalciferol only in the context of carefully audited studies.

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TABLE 1.
Clinical characteristics of each patient enrolled in to take cholecalciferol.

Patient number	Clinical Stage	Grade	Primary Treatment	Time since definitive radiation and/or surgery (months)
1	T2C	7	RT	68
2	T1C	6	RT	37
3	T2C	6	RT then orchidectomy	70
4	T2C	6	RT	52
5	T2B	6	NAA then RT	58
6	T2A	7	RP+PLND then RT	23
7	T2A	5	NAA then RP then RT	69
8	T2C	9	RP then RT	68
9	T2C	6	NAA then RP then RT	81
10	T2A	7	RP then RT	35

NAA = Neoadjuvant Androgen Ablation
RT = Radiotherapy with curative intent
RP = Radical Prostatectomy
PLND = Pelvic Lymph Node Dissection

TABLE 2.
PSA profile of each patient.

Patient number	PSA before Vitamin D	Lowest PSA after Vit D	Time to nadir (month)	Follow-up on Vitamin D (months)	Final PSA
1	2.9	1.65 *	9	9	1.65
2	4.43	3.93 *	8	10	5.15
3	1.43	1.48		10	1.87
4	2.39	2.71		7	3.11
5	4.97	4.05 *	1	5	6.47
6	3.16	1.62 *	5	5	1.62
7	0.95	0.95	9	15	1.02
8	1.06	1.34		10	1.5
9	1.71	1.6 *	1.5	3	1.65
10	0.58	0.52 *	2	11	0.88

* indicates fall in PSA since starting Vitamin D

Figure 1. Effect of Cholecalciferol upon Rate of Rise of PSA.

Rate of rise of PSA was determined by linear regression (See statistical methods)
Each point on the graph represents the rate of rise in PSA at a certain period in a patient's follow-up:
Early pre = 5th-last, 4th-last and 3rd-last PSA readings taken prior to starting Vitamin D
Late pre = 3th-last, 2nd -last and last PSA readings taken prior to starting Vitamin D
On Vitamin D = all PSA readings taken after commencing Vitamin D
Based on Wilcoxian rank-sum analysis, the rise in PSA was less while patients were on vitamin D than during either of the periods before-vitamin D (p=0.047 for "on Vitamin D" vs "early-pre" and p=.022 for "on vitamin D" vs "late-pre")