

## A Phase II Trial of Calcitriol and Naproxen in Recurrent Prostate Cancer

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**Abstract.** *Background: Androgen-deprivation therapy is commonly used in patients with progressive prostate cancer (PCa), but can be associated with unpleasant side-effects. The objective of the study was to determine whether treatment with calcitriol and naproxen is effective in safely delaying the growth and progression of PCa in men with early recurrent disease. Materials and Methods: Patients with biochemical relapse after local therapy for prostate cancer were treated with high dose calcitriol (DNI01, Novacea) (45 µg once per week) and naproxen (375 mg twice daily) for one year and followed with serum PSA levels as well as imaging studies. Results: Twenty-one patients were enrolled in the trial. Four patients met criteria for progression, with a PSA doubling time (PSADT) that decreased while on therapy. Fourteen patients had a prolongation of PSADT compared to baseline. Conclusion: Combination therapy with weekly calcitriol and daily naproxen is well tolerated by most patients and prolongation of PSADT was achieved in 75% of patients.*

Calcitriol, the hormonally active form of vitamin D<sub>3</sub>, has many actions to inhibit prostate cancer (PCa) growth and progression (1-3). Prostaglandins (PGs) have been shown to play a role in carcinogenesis and progression of many cancers including prostate cancer (PCa) (4, 5). It has been recently discovered that calcitriol regulates multiple genes involved in the PG pathway (6). These actions include calcitriol effects to decrease PG synthesis, to increase PG catabolism and to inhibit expression of PG receptors. In combination, these three mechanisms reduce PG levels and signaling thereby contributing to the attenuation of the growth stimulatory effects of PGs in PCa (3, 6).

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*Key Words:* Calcitriol, non-steroids, prostate cancer.

*Overview of prostaglandin signaling.* Compelling evidence from genetic and clinical studies indicates that increased expression of cyclooxygenase-2 (COX-2) is one of the key steps in carcinogenesis and progression (4, 5, 7). Several studies have demonstrated COX-2 overexpression in prostate adenocarcinoma and suggest a positive role for COX-2 in prostate tumorigenesis (8-11). The key enzyme responsible for the metabolic inactivation of PGs, 15-hydroxyprostaglandin dehydrogenase (15-PGDH), catalyzes the conversion of PGs to their corresponding 15-keto derivatives that exhibit greatly reduced biological activity (12). In fact, 15-PGDH has been considered to be a tumor suppressor gene (13, 14). PGs bind to G-protein coupled membrane receptors (prostanoid receptors) which activate PG signal transduction pathways (15).

*Calcitriol effects on the PG pathway in prostate cells.* Initial analyses using cDNA microarrays to study changes in the gene expression profile following calcitriol treatment of prostate cells indicated that calcitriol up-regulated the expression of 15-PGDH and down-regulated COX-2 expression (16, 17). Further study revealed that calcitriol regulated the PG pathway genes in multiple PCa cell lines as well as primary prostatic epithelial cells established from surgically removed prostate tissue from PCa patients (6). Measurable amounts of COX-2 mRNA and protein were found in various PCa cell lines as well as primary prostate epithelial cells derived from normal and cancerous prostate tissue, which were significantly reduced by calcitriol treatment (6). It was also found that calcitriol significantly increased the expression of 15-PGDH mRNA and protein in various PCa cells. It was further shown that by inhibiting COX-2 and stimulating 15-PGDH expression, calcitriol decreased the levels of biologically active PGs in PCa cells thereby reducing the growth stimulation by PGs (6). Interestingly the data also revealed that calcitriol decreased the expression of EP and FP PG receptors. The calcitriol-induced decrease in PG receptor levels resulted in the attenuation of PG mediated functional responses even when exogenous PGs were added to the cultures (6). Calcitriol suppressed the induction of the PG stimulated immediate-early gene *c-fos*

and the growth stimulation seen following the addition of exogenous PGs or the PG precursor arachidonic acid to PCa cell cultures (6). Thus, calcitriol inhibits the PG pathway in PCa cells by three separate mechanisms, decreasing COX-2 expression, increasing 15-PGDH expression and reducing PG receptors. It is believed that these actions contribute to the suppression of the proliferative stimulus provided by PGs in PCa cells. The regulation of PG metabolism and biological actions constitute an additional novel pathway of calcitriol action mediating its anti-proliferative effects in prostate cells (3).

*Combination of calcitriol and non-steroidal anti-inflammatory drugs as a therapy for PCa.* Non-steroidal anti-inflammatory drugs (NSAIDs) have the capacity to reduce PG synthesis by inhibiting COX-1 and COX-2 enzymatic activities. Several NSAIDs inhibit both the constitutively expressed COX-1 and the inducible COX-2 while others have been designed to be more selective for COX-2 (18). Since calcitriol inhibits COX-2 expression and NSAIDs act on the COX-2 protein to inhibit enzyme activity, it was hypothesized that calcitriol and a NSAID would exhibit increased potency when given in combination. It was predicted that the combination would allow the use of lower and safer concentrations of calcitriol and NSAIDs to inhibit COX-2 enzyme activity (6). In addition, an increase in the expression of 15-PGDH due to calcitriol action will lower the levels of biologically active PGs and enhance the NSAID effect. Therefore, it was hypothesized that the combination of calcitriol and NSAIDs would exhibit synergistic effects to inhibit PCa cell growth. When calcitriol was combined with the COX-2-selective NSAIDs NS398 and SC-58125 or the non-selective NSAIDs, naproxen and ibuprofen, a synergistic enhancement of growth inhibition of LNCaP and PC-3 human PCa cells was found. These results led to the further hypothesis that the combination of calcitriol and NSAIDs may have clinical utility in PCa therapy and that the combination was worthy of evaluation in a clinical trial (6).

The combination therapy approach will allow the use of lower concentration of NSAIDs and thereby minimize their undesirable side-effects. It has very recently become clear that continued use of COX-2-selective inhibitors such as rofecoxib causes an increase in cardiovascular complications in patients (19). In comparison, non-selective NSAIDs such as naproxen may be associated with fewer cardiovascular adverse effects (20). The cell data show that the combination of calcitriol with a non-selective NSAID is equally effective in inducing synergistic growth inhibition. It was therefore proposed that the combination of calcitriol with a non-selective NSAID would be a useful therapeutic approach in PCa that would allow both drugs to be used at reduced dosages leading to increased safety (6).

## Patients and Methods

This was a single arm, open label phase II study evaluating naproxen in combination with calcitriol in patients with early recurrent PCa. All patients received 45 µg of calcitriol (DN101, Novacea, South San Francisco, CA, USA) orally once a week with naproxen 375 mg twice a day and were evaluated for a biochemical PSA response and a change in PSA doubling time (PSADT). The high dose, intermittent calcitriol regimen is based on the studies of Beer and colleagues (21, 22). Patients were instructed to maintain a reduced calcium diet throughout the treatment period. Patients PSADT post intervention was compared to the baseline PSADT. Patients were monitored with serum PSA every 8 weeks and those patients who demonstrated a rise of serum PSA above 10 ng/mL over baseline, or a decrease of PSADT by half from baseline, or the need to initiate hormonal therapy, or formation of new bone lesions on bone scan, were taken off the study. The patients included were adults with histological documentation of adenocarcinoma of the prostate, who had a biochemical relapse after a radical prostatectomy or radiation therapy with normal testosterone levels. They were required to have at least three rising levels of serum PSA at least 2 weeks apart prior to the commencement of therapy. Written informed consent was obtained prior to initiation of the study procedure. The protocol was approved by the Stanford Human Subjects Institutional Review Board. Patients were excluded if they had local recurrence on a CT scan, or distant metastases by a bone scan. Hypercalcemia, history of renal stones, renal insufficiency, and those with peptic ulcers were excluded. Patients with uncontrolled hypertension or active coronary artery disease were also excluded. Prior systemic therapy for recurrence was not allowed. Those patients who had a brief course of hormonal therapy during radiation were allowed provided the testosterone level was normal. Patients were evaluated every 8 weeks with serum PSA, CBC and routine labs, serum and urine for calcium and creatinine. Testosterone levels were checked at baseline, and at completion of study. Imaging studies included a CT scan of the abdomen and pelvis at baseline to exclude nodal and local metastases, renal ultrasound for renal stones and a bone scan every 4 months.

At each visit toxicity was graded according to the National Cancer Institute common toxicity criteria (version 2.0) and recorded. Any patient with grade 4 toxicity or grade 3 toxicity persisting for more than 4 weeks was removed from the study protocol.

The primary endpoint of this prospective trial was to determine whether the PSADT was prolonged. Secondary endpoints included: PSA response, defined as the first evidence of a total serum PSA decline of >50% from baseline maintained for at least 28 days and confirmed with two consecutive measurements taken two weeks apart; and duration of sustained response, defined as time from PSA decrease of >50% from baseline to the first evidence of disease progression.

PSA responses were defined according to the consensus criteria (23). Partial response was defined by a 50% fall in serum PSA confirmed by second serum PSA 4 weeks later. Time to progression was defined as the time from first administration of study drug to the first observation of disease progression. Disease progression was defined as a rise of PSA above 10 ng/mL from baseline or a decrease of PSADT by half from baseline; initiation of hormonal therapy; or formation of new bone lesions on bone scan.

The study was designed to include 31 patients. A sample size of 31 was deemed to be sufficient to detect a response frequency (*i.e.*

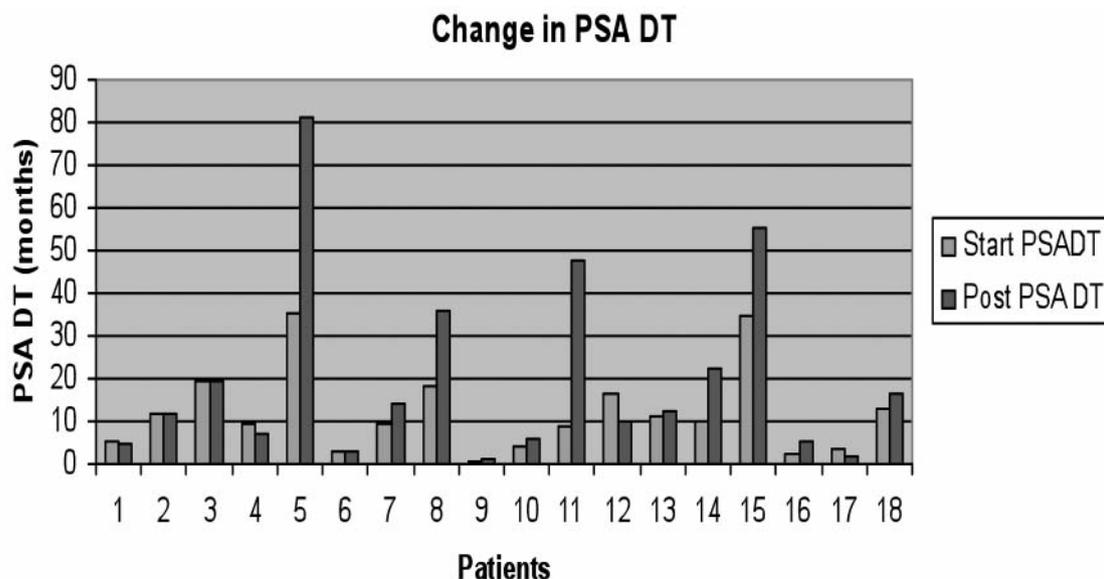


Figure 1. Change in PSA DT. The PSADT was measured before therapy (blue bars) and after therapy with calcitriol and naproxen (red bars) in 18 patients. Fourteen patients showed prolongation of the PSADT after therapy compared to baseline.

doubling of PSADT over baseline) of at least 56% compared to a null hypothesis of 28% with a power of approximately 80% and an alpha of 0.05. If there had been no responses in the first 14 patients the trial would have been stopped. If 2 out of 14 had responded then the full 31 patients would have been included. However, the trial was halted after 21 patients were enrolled when a national trial comparing DN101 in combination with weekly docetaxel had a higher death rate in the DN101 arm compared to the new standard docetaxel dosing arm (every 3 weeks) and DN101 use was suspended pending further evaluation.

Descriptive statistics were used to characterize the patients in this trial. PSA doubling time (PSADT) is the natural log of 2 divided by the slope of the relationship between the log of PSA and was calculated by the formula:  $[\log(2) \times t] / \log(\text{final PSA}) - \log(\text{initial PSA})$ , where initial PSA was the PSA at baseline and the final PSA was the last PSA prior to developing progressive disease. Pre-intervention PSADT was also calculated and compared to post-intervention PSADT. Three prior PSA values from the previous year separated by at least 3 months were used to calculate the pre-therapy PSADT.

## Results

Twenty-one patients were enrolled in the trial from 4/05-10/07 (Table I). One patient was non-compliant and not included. Median age of patients was 64 (53-78). Primary therapy was radical prostatectomy in sixteen patients. Twelve had subsequent radiation for a rising PSA. Median Gleason's score was 7 (5-10). Median number of treatment cycles was 6. Eighteen patients were evaluable for response. The mean baseline serum PSA was 6.5 (0.1-18.4) and mean PSADT was 9.5 months (0.2-54). None of the patients had bone metastases. Fifteen patients had a PSADT less than 12 months.

Table I. Patient characteristics.

Age (years)	64 (54-78)
Radical Prostatectomy	16
Radiation	5
Gleason's score	7 (5-10)
Mean PSA	6.5 (.1-18)
Mean PSA doubling time (months)	9.5 (0.2-54)
<12 months	14
12-20 months	4
>20 months	2

Four patients met criteria for progression, with a PSADT that decreased while on therapy. Three out of four had a pre-therapy PSADT <12 months. The Gleason's score was 7 in three of those patients and 9 in one patient. Fourteen patients met criteria for response and had a prolongation of PSADT compared to baseline (Figure 1). The prolongation was greater than a two-fold increase in 50% of patients. Three patients had greater than a five-fold prolongation of the PSADT. Two of these patients had a >12 month PSADT prior to commencement of therapy. No patient had a sustained drop in serum PSA to meet criteria for PSA response.

Serum creatinine and urine calcium were closely monitored in all patients. Overall, the treatment was very well tolerated. There was no evidence of gastrointestinal bleeding or drop in hemoglobin. One patient developed a small asymptomatic renal calculus detected by routine ultrasound while on therapy and was taken off the study. The urine calcium excretion was not elevated in this patient. He has not required any intervention

following discontinuation of study. One patient had grade 1 elevation of serum creatinine requiring a decrease in naproxen dose to once a day. Testosterone was maintained without any change in all patients. Three patients had gastrointestinal cramps which occurred the day after taking DN101. Two of the patients discontinued the drug in relation to the cramps.

## Discussion

Men who have a PSA relapse after primary therapy account for a third of patients with PCa (24). Optimum therapy for this group of patients is unclear. The natural history of untreated men with rising PSA after a radical prostatectomy has been reported by Pound *et al.* and usually represents an indolent biology with median time to bone metastases of 8 years (25). Hormonal therapy (androgen-deprivation therapy or ADT) often yields a clinical response, however it is usually transient and most patients eventually progress to androgen-independent PCa (26). ADT may only benefit a fraction of patients who have high Gleason's score and those with rapid PSADT of <12 months (27). While there is no survival benefit proven since almost all patients eventually escape ADT and become androgen independent (26), there may be some delay in time to clinical metastases. However, the side-effects of both short- and long-term ADT are well described and alternate therapies are clearly needed (28).

The trial reported here had the goal of delaying the progression of early recurrent PCa using a combination of two drugs that were relatively safe and would cause minimal side-effects. No therapy has been proven to be optimal at this time in the course of PCa progression and if advancement to ADT or other second-line therapy could be delayed without undue side-effects, this would be a valuable addition to the therapeutic choices for early recurrent PCa.

Fourteen patients demonstrated a prolongation of PSADT with this combination therapy; half of those had a 2-fold increase in PSADT but others had a larger increase. Although PSA levels decreased in some patients, the reduction did not fulfil criteria of a PSA response. In general, patients with a slow baseline PSADT appeared to have had a larger benefit from the therapy. A majority of patients completed one year of therapy. Four patients met criteria with a rapid increase in PSADT and were started on androgen-deprivation therapy.

These findings indicate that the combination of very high dose (45 µg) of weekly calcitriol (DN101) with daily naproxen (375 mg twice daily) was well tolerated in most patients. One patient developed a small asymptomatic renal stone. In a previous trial in similar patients using daily calcitriol at low dose as a single drug, hypercalciuria was common (29). Seven patients were treated with escalating daily doses of calcitriol. Maximum tolerated dose based on hypercalciuria was 2 to 2.5 µg per day. Six patients had slowing of the rate of rise in PSA and one patient showed a fall in PSA. There was frequent

hypercalciuria with the daily calcitriol regimen and two patients developed small asymptomatic renal stones found on routine ultrasound examination and one patient developed a stone subsequent to the trial termination.

In the current trial, 3 patients developed severe abdominal cramps on the day following the DN101 dosing. The temporal relationship suggests that combination therapy may cause cramps in some patients, perhaps because of peak prostaglandin suppression at that time-point. Symptoms resolved when the naproxen dose was decreased. Most patients tolerated the combination therapy without problems and completed the trial.

Osborn *et al.* reported a trial in men with far advanced PCa using calcitriol up to 1.5 µg daily with 2 patients having a drop in serum PSA. Hypercalciuria was dose limiting in that trial as well (30) in others by Beer *et al.* (21) and Trump *et al.* (31), where the latter investigated the pulsatile, intermittent dosing of high dose calcitriol. Beer *et al.* used up to 2.8 µg/kg without any grade 3 toxicities. They treated 22 patients with hormone naïve recurrent PCa with calcitriol 0.5 µg/kg and 3 patients demonstrated a PSA decrease of 10-47% and an improvement in PSADT (32).

The most extensive use of high-dose intermittent calcitriol was reported by Beer *et al.* in a trial of advanced androgen-independent PCa patients who had failed other therapies (22). The trial (ASCENT I) was a comparison of docetaxel alone vs. docetaxel plus calcitriol (DN101, 45 µg once weekly) with 125 patients in each arm. The striking finding was a ~50% increase in survival in the DN101 arm compared to docetaxel alone. In addition, some side-effects of the docetaxel decreased in the DN101 arm (22, 33). These promising findings led to a larger trial (ASCENT II) that employed an asymmetric trial design comparing the standard *q* 3 week docetaxel dosing regimen (34, 35) against the previously used weekly docetaxel regimen plus DN101 used in ASCENT I. Unfortunately, this trial was halted by the Data Safety Monitoring Board when an imbalance of deaths was found in the DN101 arm. The data are still being analyzed but preliminary investigation of the cause of the increased deaths suggests that they were not due to calcitriol toxicity but rather to an altered docetaxel regimen in the control arm compared to the older docetaxel regimen in the DN101 arm (34, 35).

Several groups have attempted to study alternative non-hormonal treatments for rising PSA following definitive management of PCa. COX-2 inhibitors such as celecoxib (Celebrex) have been reported by Pruthi and colleagues to slow the rate of rising PSA following radical prostatectomy or radiation therapy (36). In a placebo-controlled trial of men with biochemical recurrence, mean PSA velocity was significantly decreased in men taking celecoxib compared to placebo. (37). Unfortunately, due to an increased risk of cardiovascular morbidity, the US Food and Drug Administration halted clinical trials involving this class of drugs.

In conclusion, the results of this trial indicate that the combination of high-dose weekly calcitriol combined with naproxen has activity to slow the rate of rise of PSA measured by the PSADT in most patients. Using PSA kinetics, the best available tool for monitoring patients with biochemical relapse, the majority of patients in the trial appeared to exhibit a slowing of disease progression. The development of a therapy that delays the progression of PCa in this group of patients would be an advantage in postponing the need to use ADT or other therapies with side-effects and would therefore represent an advance over current therapy. However, the role of this combination therapy will require further study to determine its rightful place in the management of recurrent PCa.

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*Received January 29, 2009*

*Revised March 9, 2009*

*Accepted April 2, 2009*