Phase II Trial of High-Dose, Intermittent Calcitriol (1,25 Dihydroxyvitamin D3) and Dexamethasone in Androgen-Independent Prostate Cancer

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BACKGROUND. Data suggest that vitamin D plays a role in the treatment and prevention of prostate cancer. The combination of high-dose, intermittent calcitriol (1,25 dihydroxyvitamin D3) plus dexamethasone was studied based on evidence that dexamethasone potentiates the antitumor effects of calcitriol and ameliorates hypercalcemia.

METHODS. Oral calcitriol was administered weekly, Monday, Tuesday, and Wednesday (MTW), at a dose of 8 μg, for 1 month, at a dose of 10 μg every MTW for 1 month, and at a dose of 12 μg every MTW thereafter. Dexamethasone at a dose of 4 mg was administered each Sunday, and MTW weekly. Calcium and creatinine were determined weekly and radiographs of the urinary tract were performed every 3 months. All patients were considered evaluable for toxicity.

RESULTS. Forty-three men with androgen-independent prostate cancer were entered; 37 received at least 1 month of calcitriol given at a dose of 12 μg every day $\times$ 3 per week. The majority of patients had bone metastases and rising prostate-specific antigen (PSA) levels. All had an Eastern Cooperative Oncology Group performance status of 0 or 1. Eight patients (19%) experienced partial responses by PSA criterion (PSA decline of $\geq$50%, persisting for $\geq$28 days). Subjective clinical improvement occurred in some patients. Toxicity was minimal: urinary tract stones in 2 patients; and a readily reversible, CTC (v.3.0) Grade $<$2 creatinine increase in 4 patients. Throughout the study only 4 patients ever had a serum calcium level $>$11.0 mg/dL and no patient had a calcium level $>$12.0 mg/dL.

CONCLUSIONS. The response rate reported in the current study (19%) was not found to be clearly higher than expected with dexamethasone alone. High-dose intermittent calcitriol plus dexamethasone appears to be safe, feasible, and has antitumor activity. ***Cancer* 2006;106:2136–42.** *© 2006 American Cancer Society.*

KEYWORDS: calcitriol, prostate cancer, dexamethasone, Phase II trial.

1,25 Dihydroxycholecalciferol (calcitriol), the most potent vitamin D compound, is a central factor in bone and mineral metabolism and is also antiproliferative in many malignant cell types.[1–10] Calcitriol has significant antitumor activity in vitro and in vivo in murine squamous cell carcinoma (SCC); human xenograft prostatic adenocarcinoma (PC-3); rat metastatic prostatic adenocarcinoma Dunning (MLL) model systems; and human breast, colon, and pancreatic cancer, as well as leukemia, myeloma, and lymphoma lines.[3–7,9,11] Calcitriol induces G_0/G_1 arrest and modulates $p27^{Kipl}$ and $p21^{Waf1/Cipl}$.[4,12–14] Calcitriol also induces cleavage of caspase 3, polyadenyl ribose 6 phosphate (PARP), and the growth-promoting/prosurvival signaling molecule mitogen-activated protein kinase (MEK) in a caspase-dependent manner.[9,11] In association with these effects, full-length MEK

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and phospho-Erk (P-Erk) are lost. Calcitriol inhibits the phosphorylation and expression of Akt, a kinase regulating an important cell survival pathway. In contrast to changes that occur during cytotoxic drug-induced apoptosis, the proapoptotic signaling molecule MEKK-1 is significantly up-regulated by calcitriol.[9]

We have demonstrated that dexamethasone potentiates the antitumor effect of calcitriol and decreases calcitriol-induced hypercalcemia.[13,14] Both in vitro and in vivo, dexamethasone significantly increases vitamin D receptor (VDR) ligand binding in the tumor, while decreasing binding in intestinal mucosa, the site of calcium absorption.[13–15] Phospho-Erk (P-Erk) and phospho-Akt (P-Akt) are also decreased more with the combination of calcitriol and dexamethasone than with either agent alone.[14]

These preclinical data in conjunction with the considerable need to develop new therapeutic approaches for prostate cancer led us to evaluate a regimen of high-dose oral calcitriol and dexamethasone administered on an intermittent schedule. We had previously shown that subcutaneous calcitriol administered at a dose of 8 μg every other day was safe and feasible (average weekly total dose of 28 μg).[16] These data as well as preliminary pilot experience suggesting that high-dose calcitriol at a dose of 12 μg daily given $\times$ 3 plus dexamethasone weekly would be well tolerated led us to evaluate this regimen in men with androgen-independent prostate cancer (AIPC) for safety and activity.

MATERIALS AND METHODS

Patient Eligibility Criteria

Patients eligible for this trial were those in whom prostate cancer was progressive despite androgen deprivation. Patients were required to have evidence of progressive disease as manifested by new radiographic lesions on bone scan or computed tomography (CT) scan and/or PSA increasing by >50% compared with nadir achieved with androgen deprivation and clearly rising on 3 successive values each more than 2 weeks apart over 6-8 weeks before entry, despite gonadal suppression (surgical or medical castration) and antiandrogen withdrawal, as appropriate (4 weeks for flutamide, and 6 weeks for bicalutamide). Performance status was required to be 0, 1, or 2 according to the criteria of the Eastern Cooperative Oncology Group (ECOG). Patients were required to have normal hematologic and organ function parameters (white blood cell count >4000/mm^3, a platelet count >100,000/mm^3, creatinine < 1.6/dL, bilirubin <1.5 mg/dL, and aspartate aminotransferase and alanine aminotransferase within normal limits). The corrected serum calcium was required to be <10.5 mg/dL. Patients with any history of nephrolithiasis were ineligible and all patients were required to have either a CT scan or ultrasound (US) examination of the kidneys and ureters that indicated no evidence of lithiasis within 30 days of study entry. There was no restriction on entry based on extent of prior therapy if other entry criteria were satisfied. Prior anticancer therapy with calcitriol or calcitriol analogs was not allowed. The maximum dose administered was 12 μg given every day $\times$ 3 because at the time the current study was conducted we believed this was the maximum safe dose. Informed written consent was required and this study was approved by the University of Pittsburgh Biomedical Institutional Review Board.

Treatment Plan

Calcitriol (Rocaltrol, Roche Pharmaceuticals, Indianapolis, IN) was obtained from commercial sources as either 0.5-μg or 0.25-μg caplets and was administered according to the following schedule: 8 μg given on Monday, Tuesday, and Wednesday (MTW) $\times$ 4 weeks, 10 μg given MTW $\times$ 4 weeks, and then 12 μg given MTW weekly thereafter. The calcitriol dose was escalated after 1 month if no dose-limiting therapy occurred. Dexamethasone was given at a dose of 4 mg orally on Sunday and MTW. Calcitriol was administered at bedtime and dexamethasone was administered at noon. Dietary calcium was not restricted during the study. The choice of this treatment plan was based on our prior studies of calcitriol that demonstrated that intermittent therapy was better tolerated than continuous therapy, that 28 μg/week was the maximum tolerated dose (MTD) on a every-other-day subcutaneous schedule, and a small pilot experience demonstrating that this dose and schedule appeared to be safe. This regimen was approached with caution, however, because at the time this was the highest dose of calcitriol ever given. Our prior work indicated that calcitriol toxicity was evident within 30 days of treatment initiation; therefore, the dose was escalated monthly to 12 μg given daily $\times$ 3 weekly. Dexamethasone dose was chosen based on our prior experience with calcitriol plus dexamethasone[16] and was roughly equivalent to the murine dose shown to potentiate calcitriol. The schedule for dexamethasone was chosen to provide potentially potentiating dexamethasone with calcitriol rather than continuous dexamethasone.

Patient Monitoring and Dose Modification

Serum calcium, phosphorus, creatinine, and electrolytes were measured on the Thursday of each week; liver function tests and hematologic values were de-

termined monthly, and US or CT evaluation for urinary tract stones was repeated every 3 months. When a symptomatic bladder stone was discovered in Patient 18 after 411 days of therapy, it was realized that monitoring US examinations did not routinely include the bladder; subsequently, all patients underwent US of the kidney, ureter, and bladder. PSA was determined monthly and radiographs to assess response were repeated every 3 months. In patients whose serum calcium was >11.5 mg/dL on Thursday, the serum calcium measurement was repeated on Monday. If the serum calcium measurement on Monday was ≤11.5mg/dL, treatment was continued without dose or schedule modification. If the serum calcium remained >11.5 mg/dL, calcitriol was held and calcium measurement was repeated on Thursday and Monday. Therapy was resumed at the same dose and schedule on the next Monday that the serum calcium was <11.5mg/dL. If a patient required 2 such dose interruptions, the calcitriol dose was to be reduced by 50% when therapy was resumed. Because to our knowledge this was the highest dose of calcitriol ever given in prostate cancer patients at the time the current study began, toxicity was monitored very closely.

Statistical Design

This study was designed as a 2-stage Phase II trial, in which 19 patients were to be accrued in the first stage and 16 in the second. Good and poor response rates were established at 35% and 15%, respectively; the Types I and II errors were 15% and 5%, respectively. Responses were evaluated according to standard ECOG criteria for measurable disease response assessment (partial response [PR] was considered to be a ≥50% decrease in the sum of the products of bidimensional measurements of all measurable lesions; and complete response [CR] was considered to be the complete disappearance of all lesions) and PSA response was considered to have occurred if a PSA decrease of 50% was sustained for ≥28 days. To determine response after the highest dose of calcitriol administered, patients were considered evaluable for response assessment if they received at least 1 month of calcitriol at a dose of 12 μg given every day × 3 weekly × 4; patients who did not satisfy this criterion were replaced. Progressive disease was not considered to have occurred during Months 1, 2, or 3 unless symptomatic and/or radiographic disease progression occurred. An increase in PSA during the first 3 months was not a criterion for progression. This approach was taken for 2 reasons: 1) there are in vitro data indicating that calcitriol causes the release of PSA from prostate cancer cells, suggesting that short-term changes in PSA may not reflect antitumor effects; and 2) we wished to evaluate PSA and clinical response at the highest dose of calcitriol possible. The duration of response was calculated as the interval between the date when a ≥50% decrease in PSA was observed and the date on which the PSA increased by ≥50% above the nadir PSA.

TABLE 1
Patient Characteristics (n = 43)

Prior therapy		
Medical castration plus antiandrogen	31	
Orchiectomy	15	
Secondary hormonal therapy		
Antiandrogen only	7	
≥2 agents	15	
Prior cytotoxic therapy*		
1 regimen	4	
2 regimens	1	
Pain requiring narcotic analgesics	25	
Bone metastases	38	
Soft tissue metastases	11	
Median age, y (range)	69	44-82
Median PSA (range)	60.6 μg/mL	4-744.8
Median alkaline phosphatase (range)	1248 IU/mL	8-2520
Median hematocrit (range)	39.3%	30.3-48.4%

PSA: prostate-specific antigen.
* Mitoxantrone (2 patients), estramustine phosphate (1 patient), cyclophosphamide (1 patient), and mitoxantrone and docetaxel (1 patient).

RESULTS

Patient Characteristics

Patient characteristics are shown in Table 1. Forty-three patients were entered into study between September 1998 and July 2000. All patients had an ECOG performance status of 0 (25 patients) or 1 (18 patients). The median age was 69 years (range, 44-82 years), and all patients had evidence of progressive disease despite androgen deprivation and antiandrogen withdrawal of appropriate duration. A total of 31 patients had received medical castration plus an antiandrogen, 15 had undergone orchiectomy (3 patients were surgically castrated after having undergone medical castration), 7 had received a subsequent single-agent antiandrogen, 15 received ≥2 hormonal manipulations, 4 had received 1 cytotoxic regimen, and 1 patient had received 2 cytotoxic regimens. One patient was receiving a bisphosphonate. The median PSA was 60.6 μg/mL (range, 4-744.8 μg/mL). Twenty-five patients

TABLE 2
Toxicity Associated with Calcitriol/Dexamethasone Therapy (n = 43)

	Grade ≥2	Grade 3	Grade 4
Hematopoietic	None	None	None
Renal	4.6%	None	None
Hepatic	None	None	None
Musculoskeletal	None	None	None
Neurologic	None	None	None
Gastrointestinal	None	None	None
Cardiopulmonary	None	None	None
Hyperglycemia	2.3%	2.3%	None

were receiving analgesics for pain at the time of study entry. Thirty-eight patients had bone metastases at the time of study entry and 11 had soft tissue metastases detected by CT. Thirty-five patients were eligible for response evaluation, having completed 3 months of calcitriol/dexamethasone therapy (1 month at a dose of 12 μg every day × 3 weekly × 4). Eight patients did not complete 3 months of therapy for the following reasons: consent withdrawn in 3 patients; symptomatic, disease progression in 4 patients; and glucocorticoid toxicity in 1 patient. Disease progression in these 4 patients consisted of symptomatic progression in bone metastases requiring irradiation.

Response Assessment

No patient met the criteria for soft tissue disease response (11 patients were evaluable for soft tissue response). Eight of 43 patients (18.6%) experienced and maintained for ≥28 days a decrease in PSA of >50% (median decrease, 64%; range, 55-92%). All 8 patients received at least 1 month of 12 μg of calcitriol given MTW. Time from PSA nadir to a 50% increase (duration of PSA response) was generally short, with a median of 28 days (range, 22-143 days). In 1 additional patient whose PSA fell by >73%, confirmation of persistent decline for >1 month was not achieved because the patient died 6 weeks after the initiation of therapy due to a pulmonary embolism believed to be unrelated to therapy.

Toxicity

Toxicity was assessed using the National Cancer Institute's Common Toxicity Criteria (version 3.0). Aside from a single patient who developed Grade 3 hyperglycemia within 1 month of beginning therapy, there were no toxicities >Grade 2 associated with protocol treatment (Table 2). All Grade 1 and Grade 2 toxicities were readily and rapidly reversible without treatment interruption.

Serum Calcium

Forty-three patients were on study for a total of 5451 days and 806 weekly serum calcium values were assessed. Fifty-three serum calcium values were >11 mg/dL (6.6%) and 6 serum calcium values were >12 mg/dL (0.7%). In 8 patients (18.7%), serum calcium levels between 11 mg/dL and 12 mg/dL were detected on ≥1 occasions, and in 3 patients (6.9%) calcium levels >12 mg/dL were detected. The study design mandated interruption of every day × 3 weekly calcitriol dosing for a persistent serum calcium increase (>11.5 mg/dL for ≥5 days) unless symptoms or complications associated with hypercalcemia were noted. Patients with symptomatic hypercalcemia were to cease therapy and resume treatment at a lower dose. The criteria for dose reduction/interruption based on hypercalcemia were not met in any patient.

Urinary Tract Stones

In 2 patients, urinary tract stones were diagnosed after 179 days (Patient 4) and 411 days (Patient 18) of therapy. In Patient 4, a stone was diagnosed by US of the upper tract. This patient was totally asymptomatic. In Patient 18, the occurrence of hematuria and dysuria were followed by cystoscopic examination, which confirmed a bladder stone. Both patients were removed from the current study because of the development of urinary tract stones. In Patient 37, a bladder stone was suspected because of new irritative voiding symptoms and hematuria. Although these symptoms resolved spontaneously, this patient had evidence of progressive disease; therapy was discontinued and the suspicion of a bladder stone was never confirmed.

Renal Function

Based on prior studies, hypercalcuria was expected to be universal with this regimen.[16,17] Patients were carefully monitored for renal dysfunction. Among 43 patients with advanced prostate cancer, Grade 2 renal toxicity (serum creatinine 1.5-3.0 times the upper limit of normal) occurred in only 2 patients (4.6%). These patients were among the 35 patients who received >3 months of high-dose calcitriol therapy and represent 5.7% of that population. Single serum creatinine values of 2.4 mg/dL (Patient 6 at Day 289) and 2.3 mg/dL (Patient 27 at Day 112) were noted. In Patient 6, the serum creatinine was 1.9 mg/dL 1 week later and did not increase to >2.1 mg/dL for the remaining 45 days the patient remained on study. In Patient 27, calcitriol was withdrawn when a creatinine level of 2.3 mg/dL was noted; 1 week later the creatinine level was 1.9 mg/dL and calcitriol administration was resumed; the creatinine did not reach Grade 2 toxicity criteria dur-

ing the remaining 40 days the patient was on study. Therefore, renal toxicity was uncommon, transient, and nonrecurring in each patient. No renal dysfunction >Grade 2 was observed.

DISCUSSION

Considerable preclinical data suggest that vitamin D may be useful as an antiproliferative agent in clinical cancer management.[1–4] Our preclinical studies clearly indicate a steep dose-response relation for vitamin D antitumor effects.[3,11–13] Initial clinical studies of vitamin D focused on hematologic malignancies and utilized daily oral dosing regimens. Limited indications of efficacy and worrisome increases in serum calcium were noted.[18,19] Osborn et al.[20] reported a trial of calcitriol in AIPC patients administered on a every-day schedule (1.0-1.5 μg every day). No responses were noted and a 30% frequency of hypercalcemia was encountered. Since these initial studies were performed, we and others have shown that intermittent, high-dose calcitriol regimens are safe and feasible.[16,21,22] Beer et al.[21] reported that high-dose weekly oral calcitriol is well tolerated at doses up to 2.6 μg/kg/wk and Morris et al.[22] noted that calcitriol up to 30 μg given every day $\times$ 3, weekly plus zoledronic acid was safe. Because the antitumor effects noted in in vivo models are observed with intermittent schedules and the safety of these regimens is now clear, recent clinical trials have evaluated intermittent, high-dose vitamin D analogs in cancer therapy.[16,21–24]

To our knowledge, the MTD of calcitriol in advanced cancer patients is unknown. Definition of the MTD would allow evaluation of the clinical activity of the maximal safe dose and would also determine whether the systemic exposure that results in antitumor activity in preclinical models can be achieved in patients.[25] At the time the current trial was initiated, there were no data regarding the safety of high-dose, oral, intermittent calcitriol. The dose and schedule employed were chosen based on our prior work with subcutaneous calcitriol and limited pilot data indicating that this regimen, which was believed to be an aggressive dosing schedule, appeared to be safe. Because there is still considerable concern regarding the safety of high-dose calcitriol and many argue there is the need to develop analogs that are less inclined to cause hypercalcemia, we believe that an in-depth discussion of these issues is warranted. To our knowledge, there are no other published data regarding this dose and schedule of calcitriol. Data from the current study and those of Beer et al.[21] and Muindi et al.[23] indicate that doses higher than those used here are inconsistently and erratically absorbed. There are several challenges to determining the calcitriol MTD. The absorption of the currently available formulations appears to be limited at high oral doses. In addition, it is not clear what is an acceptable or tolerable degree of modification of calcium metabolism among patients, especially patients with advanced cancer. Some studies of calcitriol administration have limited calcitriol dosing based on the occurrence of hypercalcuria.[17] An increase in urine calcium is universal in patients receiving intermittent high-dose calcitriol. Based on the current study, as well as previously reported trials, there is little evidence that intermittent hypercalcuria, unaccompanied by any other biochemical change, has unacceptable consequences in patients with advanced cancer studied over a relatively short period of time (3-12 months).[16,21–24] The current study and others suggests that a 6-month to 12-month treatment with intermittent high doses of calcitriol infrequently causes urinary tract stones. Hypercalcemia can cause clinical symptoms; however, the health consequences of intermittent, mild hypercalcemia are uncertain. In the current study, as well as those of other authors,[21–28] it is unusual for serum calcium levels >11.0 mg/dL to occur; furthermore, such increases are transient and often do not recur despite continued calcitriol administration.

The current study was initiated before it was clear that substantial dose escalation of oral calcitriol was possible and before the problem of incomplete absorption of oral calcitriol was evident. Our initial studies had shown that daily calcitriol administration resulted in symptomatic or clinically significant hypercalcemia in 30% of patients (dose intensity [DI] of 22 μg/14 days). A subsequent study of subcutaneous calcitriol demonstrated that a dose of 10 μg given every other day resulted in hypercalcemia in all patients (DI of 70 μg/14 days). The regimen in the current study (DI of 72 μg/14 days) achieved the administration of high doses of calcitriol without limiting toxicity.

This regimen was very well tolerated. Our studies have shown that calcitriol at a dose of 38 μg every day $\times$ 3 weekly plus paclitaxel (80 mg/m^2) causes no hypercalcemia. Our studies and those of Muindi et al.[23,26] also clearly demonstrated that, at doses >14 μg to 18 μg, the correlation between the administered dose and the concentration in blood is no longer linear, suggesting a dose-related limitation of bioavailability at higher doses. We have observed this loss of dose-proportional increase in blood level with both commercially available caplet and liquid palm oil formulations. The regimen described in the current study was extremely well tolerated and permitted the administration of higher doses of calcitriol than we had previously achieved. Based on our preclinical studies,

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