High-Dose Calcitriol, Zoledronate, and Dexamethasone for the Treatment of Progressive Prostate Carcinoma

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BACKGROUND. Preclinical and clinical data have suggested that high-dose calcitriol (1,25-dihydroxycholecalciferol) has activity against prostate carcinoma. Pulse-dosed calcitriol and dexamethasone may maximize tolerability and efficacy. The authors examined the toxicity of pulse-dosed calcitriol with zoledronate and with the addition of dexamethasone at the time of disease progression.

METHODS. Patients with progressive prostate carcinoma were eligible for the current study. In cohorts of 3–6 patients, calcitriol was administered for 3 consecutive days per week, starting at a dose of 4500 IU per day. Doses were escalated to 3000 IU per day. Intravenous zoledronate (4 mg) was administered monthly. Dexamethasone could be added to the regimen at disease progression. Toxicities, markers of bone turnover, plasma calcitriol levels, and clinical outcomes were recorded.

RESULTS. Thirty-one patients were treated in cohorts that were defined by the calcitriol dose administered (4, 6, 8, 10, 12, 19, 20, or 30 IU). Seven patients received dexamethasone. Three patients had their doses reduced due to calcium-related laboratory findings. Patients tolerated therapy well, even in the 30 IU cohort; therefore, a maximum tolerated dose was not defined. Peak plasma levels observed in the 24 IU and 30 IU cohorts ranged from 391 to 968 pg/mL. Minimal antitumor effects were observed.

CONCLUSIONS. Calcitriol was well tolerated at doses up to and including 30 IU 3 times per week in combination with intravenous zoledronate 4 mg monthly, with or without dexamethasone, in patients with progressive prostate carcinoma. Peak plasma levels in the 24 IU and 30 IU cohorts were greater than the levels associated with antitumor effects preclinically. Due to the cumbersome dosing schedule and the lack of significant activity observed, Phase II trials of this regimen are not planned. Cancer 2004;100:1868–75. © 2004 American Cancer Society.

KEYWORDS: vitamin D, bisphosphonates, steroid hormones, prostate carcinoma.

Preclinical studies have demonstrated that calcitriol (1,25-dihydroxycholecalciferol) participates in the regulation of apoptosis, cell cycle arrest, and cellular differentiation in a number of different malignancies.1–4 These effects are mediated in part by the vitamin D3.
receptor (VDR), a member of the steroid hormone receptor superfamily that forms heterodimers with the retinoid-X receptor. The hypothesis that vitamin D metabolism may play a role in prostate carcinoma growth and development was proposed over a decade ago when Schwartz and Hulka observed that the incidence of prostate carcinoma varied inversely to ultraviolet exposure. When bound to calcitriol, the VDR is phosphorylated and then functions as a transcription factor. However, calcitriol appears to have effects on the cell that are independent of the VDR as well, such as the direct modulation of cell signal transduction. Both androgen-dependent and androgen-independent cell lines express the VDR, and calcitriol inhibits tumor growth in prostate cell cultures and animal models. Several clinical studies have been conducted to determine the toxicity profile, optimal dosing schedule, and preliminary efficacy of calcitriol in patients with prostate carcinoma. Two Phase II studies that used intrapatient escalating daily doses of calcitriol of 0.5–2.5 µg found that calcitriol could alter prostate-specific antigen (PSA) kinetics favorably. However, low-grade hypercalcemia and hypercalciuria were observed and were considered to be dose limiting. Other investigators found that pulse-dosing of calcitriol allowed the administration of higher doses. A preliminary report by Trump et al. suggested that calcitriol dosing as high as 12 µg 3 times per week in combination with dexamethasone was tolerated well. In another trial, weekly dosing of 0.06–2.8 µg/kg produced no significant toxicity. Additional preclinical data suggested that dexamethasone can enhance the antitumor effects of calcitriol. In squamous cell cultures and xenograft models, dexamethasone enhanced VDR expression and increased cell kill.

On the basis of these data supporting pulse-dosing and the use of dexamethasone with calcitriol, we conducted a Phase I dose-finding trial using pulse-dosed calcitriol. To minimize the effects of hypercalcemia, we combined the calcitriol with zoledronate, a bisphosphonate that has now been approved by the U.S. Food and Drug Administration for the treatment of patients with metastatic disease in bone. If patients demonstrated evidence of progressive disease on calcitriol and zoledronate alone, then dexamethasone could be added to the regimen at the discretion of the treating physician.

MATERIALS AND METHODS

Patients

The protocol was approved by the Institutional Review Board at Memorial Sloan-Kettering Cancer Center (New York, NY), and all patients signed informed consent forms before registration. Cohort 1 received calcitriol alone. The protocol was amended to allow patients in Cohort 2 and later cohorts to receive zoledronate. The protocol was amended further to allow patients in Cohort 4 and later cohorts to receive dexamethasone in the event of disease progression.

Patients could register for the trial if they had received primary treatment for localized disease with either radiation or surgery and now had an increasing PSA level in the absence of radiographically or scintigraphically evident disease; they had progressive radiographically or scintigraphically evident metastatic disease with noncastrate testosterone levels; or they had progressive metastatic disease in the setting of castrate testosterone levels (i.e., ≤ 30 ng/dL). In this third category, patients receiving primary hormone therapy who were using an antiandrogen were required to have experienced progression despite antiandrogen withdrawal. For all patients, biochemical progression was defined as 3 increases of > 50% in the PSA level over at least 2 weeks. New bone lesions or an increase of > 25% in bidimensional soft tissue metastases qualified as disease progression in patients with metastases.

Other eligibility requirements included a Karnofsky performance status ≥ 70% and adequate organ functioning as evidenced by a white blood cell count ≥ 3500/mm³, a platelet count ≥ 100,000/mm³, bilirubin < 2 mg/dL, creatinine ≤ 1.6 mg/dL, or creatinine clearance ≥ 60 mL per minute. Patients with preexisting endocrine or metabolic disorders that impacted the calcium-regulatory axis, including hypercalcemia or hypercalciuria, were excluded, as were patients with a history of recurrent nephrolithiasis, malabsorption syndromes, or inflammatory bowel diseases.

Treatment Schedule

Patients were assigned to cohorts of 3–6 patients. Each cohort was defined by the calcitriol dose administered: 4, 6, 8, 10, 14, 20, 24, or 30 µg taken orally before bedtime on Days 1, 2, and 3 of each week. Patients in the 6 µg cohort and those in cohorts receiving higher doses also received zoledronate (Zometa; Novartis Pharmaceuticals, East Hanover, NJ) 4 mg intravenously over 15 minutes on Day 1 of each month of treatment. Patients in the 10 µg cohort and those receiving higher doses could also receive dexamethasone 0.75 mg orally twice daily if their PSA levels increased by > 50% or if progressive disease was noted on imaging scans while only calcitriol and zoledronate were being administered.

When data became available regarding the pharmacokinetics of pulse-dosed calcitriol, the study was
amended, mandating that patients take calcitriol on the morning of Day 1 so that peak plasma levels could be assessed more precisely 3–6 hours after receiving the drug. This strategy was adopted as patients were entering the 30 µg cohort.

If no Grade 3 or 4 toxicities were observed after 2 weeks of treatment, then a new cohort was treated. Calcitriol was provided in the form of 0.5 µg capsules (Rocaltrol; Roche Laboratories, Nutley, NJ). Doses were rounded to the nearest tablet. Patients were instructed to take no supplemental vitamin D and to maintain low-calcium diets (< 800 mg calcium daily). Dietary guidelines were provided. Dose escalations were planned to continue until dose-limiting toxicity (DLT) occurred in two of three patients or in two of six patients, at which point the maximum tolerated dose (MTD) would be defined as the dose used in the previous cohort.

**DLT and Dose Attenuation Schedule**

Calcitriol was held for 2 weeks if the corrected serum calcium level was ≥ 11.5 mg/dL, if the 24-hour urine calcium level was ≥ 350 mg per 24 hours, if the urine calcium:creatinine ratio was ≥ 0.35, or if the calcium and phosphorous product was > 60. The protocol was amended later, because it was believed that the definition of hypercalciuria was unduly restrictive. Hence, the 24-hour urine calcium level was eliminated as a defining factor for DLT, and dose-limiting hypercalciuria was defined only by a calcium:creatinine ratio ≥ 0.35. In addition, ionized calcium levels were eliminated as a defining criterion for DLT, and only a serum-corrected calcium level ≥ 11.5 mg/dL was used to define DLT in terms of hypercalcemia. If the DLT resolved, then calcitriol administration was reinitiated at a 50% dose reduction. If these abnormalities recurred, then the patient was removed from the trial.

Dose-limiting hypercalcemia was defined as a corrected calcium level of < 7.5 mg/dL, which prompted a 50% dose reduction in zoledronate. If the corrected calcium dropped below 7 mg/dL, then zoledronate was held.

If a patient’s creatinine concentration was < 1.4 mg/dL at the time of study entry, then an increase of ≥ 0.5 mg/dL prompted a suspension of treatment with calcitriol and zoledronate until the creatinine level returned to baseline. Patients with baseline creatinine levels ≥ 1.4 mg/dL were allowed an increase of 1 mg/dL, after which treatment was held. Patients who developed pancreatitis or nephrolithiasis were withdrawn from the study.

**Study Evaluations**

**Serology**

Patients’ calcium and phosphorous levels were monitored weekly. Physical examinations were performed every 2 weeks along with assays for PSA, acid phosphatase, albumin, and creatinine. Bone alkaline phosphatase (BAP), N-telopeptide, parathyroid hormone, urinary calcium, and creatinine excretion were measured every 4 weeks.

**Calcitriol levels**

Assays of calcitriol levels were performed every 2 weeks for all patients. Serum was extracted with acetonitrile and was assayed using an equilibrium radioimmunoassay procedure (DiaSorin, Stillwater, MN) involving a goat anti-25-OH-vitamin D antibody along with an iodinated (125I) analog of 25-OH-vitamin D and donkey anti-goat antibody as a precipitating complex. The normal reference range for this assay in our laboratory is 9.0–37.6 ng/mL.

Data regarding the pharmacokinetics of pulsedosed calcitriol became available toward the end of the study and suggested that the drug is absorbed rapidly and then cleared. We then amended the protocol to capture peak plasma calcitriol levels on Day 1 of Week 5 for the 30 µg cohort (and for patients in other cohorts who were still on study at that time). These levels were measured 3–6 hours after patients ingested the calcitriol.

**Outcome assessments**

One cycle of therapy was defined as 12 weeks of treatment with restaging occurring on Week 12. Bone scans and helical computerized tomography scans were performed every 12 weeks, with thin cuts through the kidneys to rule out nephrolithiasis. Patients with only an increasing PSA level continued on study if they had no new findings on bone scans or soft tissue imaging and if their PSA level had not exhibited 3 consecutive increases to > 50% above baseline at 12 weeks.

Patients with established bone metastases continued to receive therapy if imaging showed no new bone or soft tissue disease and if their PSA levels had not increased more than 3 times consecutively to > 50% above baseline. Soft tissue lesions were considered to have progressed if an increase of > 25% in the sum of the longest perpendicular dimensions of the indicator lesions, the appearance of new lesions, or 3 successive increases in PSA level to > 50% above baseline were observed. Because calcitriol can behave as a differentiation agent, we considered the possibility that the PSA level could increase at least initially despite the fact that the patient was responding to therapy.
Hence, in the event that tissue disease regressed, bone lesions appeared to improve, or the patient otherwise appeared to be benefiting clinically, he would remain on study even if his PSA level increased on 3 consecutive occasions to > 50% above baseline.

**Biostatistical Considerations**

The primary objective of the current Phase I study was to define the MTD of calcitriol and zoledronate, i.e., the dose level before which at least two of three patients or two of six patients experienced DLT. If one of the initial three patients at a given dose level experienced DLT, then three additional patients would be treated at the same dose level. Dose escalation would continue if no more than one of the six patients who were entered at the dose level experienced DLT. If two or three of the first three patients experienced DLT, or if two or more of the six patients total at a given dose level experienced DLT, then the MTD would be defined as the preceding dose level. If only three patients were treated at a dose that was under consideration as being the MTD, then an additional three patients would be treated at that level to confirm the previous results. DLT was defined as hypercalcemia or hypercalciuria as defined above or as Grade 3 nonhematologic or Grade 4 hematologic toxicity (according to the National Cancer Institute Common Toxicity Criteria, Version 2.0) occurring at any time during treatment. All patients were evaluable for toxicity.

**RESULTS**

**Patients**

Thirty-two patients were registered, and 1 patient was not treated because his PSA level decreased spontaneously before treatment. Thus, 31 patients were treated and were evaluable for toxicity and outcome (Table 1). Twenty-eight patients (90%) had metastatic disease, and 3 patients (10%) had increasing PSA levels (only) after radical prostatectomy or radiotherapy. Of the 28 patients with metastatic disease, 12 (39%) had noncastrate testosterone levels, and 16 (52%) had progressive disease despite having castrate testosterone levels. Among the latter group, 10 patients had been treated previously with chemotherapy.

**Treatment**

The cohorts were defined by the following doses of calcitriol: 4 μg, 6 μg, 8 μg, 10 μg, 14 μg, 20 μg, 24 μg, and 30 μg on Days 1, 2, and 3 of every week. Zoledronate was added beginning with Cohort 3, and the dexamethasone crossover was added beginning with Cohort 4. Table 2 describes the cohorts and patient numbers. Thus, 7 patients received calcitriol alone; 17 patients received both calcitriol and zoledronate; and 7 patients received calcitriol, zoledronate, and dexamethasone. Patients received a median of 12 weeks of treatment (range, 6–84 weeks). One patient with castrate testosterone levels remains on study after having completed seven treatment cycles.

Cohort 1 was expanded to include 6 patients, because 1 patient experienced hypercalcemia by virtue of

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing PSA only (no metastases)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Metastatic disease, noncastrate testosterone levels</td>
<td>12 (39)</td>
</tr>
<tr>
<td>Metastatic disease, castrate testosterone levels</td>
<td>16 (52)</td>
</tr>
<tr>
<td>Age (yrs) Median</td>
<td>70</td>
</tr>
<tr>
<td>Range</td>
<td>51–80</td>
</tr>
<tr>
<td>KPS Median</td>
<td>90</td>
</tr>
<tr>
<td>Range</td>
<td>80–100</td>
</tr>
<tr>
<td>PSA (ng/mL) Median</td>
<td>76.95</td>
</tr>
<tr>
<td>Range</td>
<td>5.12–1854.0</td>
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<tr>
<td>Prostatic acid phosphatase (ng/ml) Median</td>
<td>4.5</td>
</tr>
<tr>
<td>Range</td>
<td>0.8–470.0</td>
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<tr>
<td>Hemoglobin (g/dl) Median</td>
<td>14.2</td>
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<tr>
<td>Range</td>
<td>8.3–16.3</td>
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<tr>
<td>Alkaline phosphatase (units/L) Median</td>
<td>14.2</td>
</tr>
<tr>
<td>Range</td>
<td>8.3–16.3</td>
</tr>
</tbody>
</table>

KPS: Karnofsky performance status; PSA: prostate-specific antigen.

<table>
<thead>
<tr>
<th>Cohort</th>
<th>No. of patients in cohort</th>
<th>Calcitriol dose TIW (μg)</th>
<th>Zoledronate dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>4</td>
<td>—</td>
</tr>
<tr>
<td>2a</td>
<td>1</td>
<td>6</td>
<td>—</td>
</tr>
<tr>
<td>2b</td>
<td>3</td>
<td>6</td>
<td>4</td>
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<td>3</td>
<td>3</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>3*</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>6*</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>3*</td>
<td>24</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>3*</td>
<td>30</td>
<td>4</td>
</tr>
</tbody>
</table>

TIW: three times per week.

*One crossover to dexamethasone.

*Four crossovers to dexamethasone.
an elevated ionized calcium level (5.5 mg/dL), while another patient developed elevated urinary calcium levels (616 mg per 24 hours). Both patients were asymptomatic. After this cohort expansion, the criteria by which hypercalcemia and hypercalcuria were defined were liberalized, as described above. The 20 μg cohort accrued 6 patients, but not due to an observed toxicity. Instead, these additional patients were accrued to explore further whether significant hypercalcemia would be observed at higher doses of calcitriol. Subsequent cohorts held only 3 patients, because hypercalcemia was not observed in the 6 patients who were treated in the 20 μg cohort.

An MTD was not reached in the current study, as the 30 μg dose was well tolerated and the regimen proved to be prohibitively unwieldy at higher doses. Therefore, dose escalations were not performed at doses > 30 μg.

### Adverse Events

#### Metabolic

Table 3 summarizes the adverse events observed in the study. Two patients had their doses reduced due to hypercalcemia. One patient in the 4 μg cohort who received calcitriol alone had his dose reduced due to an elevated ionized calcium level of 5.5 mg/dL (normal, 4.8–5.3 mg/dL); his total calcium level remained within normal limits (10.5 mg/dL; normal range, 8.5–10.5 mg/dL), and he was asymptomatic. The trial subsequently was amended to eliminate elevated ionized calcium levels as a DLT, as discussed above. Another patient in the 20 μg cohort who was treated with calcitriol, zoledronate, and dexamethasone had his dose reduced due to Grade 2 hypercalcemia in Cycle 5 during Week 3. He later exhibited radiographic (but not clinical) evidence of nephrolithiasis and was withdrawn from the study.

Another patient had his dose reduced due to hypercalciuria. He had been assigned to the 20 μg calcitriol, zoledronate, and dexamethasone cohort, and he was found to have an elevated 24-hour urinary calcium level of 365 mg (normal, 50–150 mg per 24 hours). Because his creatinine:calcium ratio was normal, a dose reduction was not required according to the protocol; however, his dose was in fact reduced by his treating physician.

Other calcium-related events were observed but did not prompt dose reductions. One patient had an elevated calcium:creatinine ratio (0.36), which was evaluated as being normal at a confirmatory testing of urine electrolytes. Seven patients had elevated 24-hour calcium levels, ranging from 359 to 783 mg calcium per 24 hours, without evidence of nephrolithiasis or other sequelae. No patients developed Grade 3–4 hypocalcemia, and none developed an elevated calcium-and-phosphate product.

Eight patients developed Grade 3 hypophosphatemia. This finding was unexpected, because the physiologic effects of calcitriol should induce hyperphosphatemia rather than hypophosphatemia. Because hypophosphatemia is nonphysiologic in relation to calcitriol, cohorts were not expanded on the basis of this finding. Hypophosphatemia is a known and expected side effect of zoledronate.

#### Hematologic, musculoskeletal, pulmonary, gastrointestinal, renal, and other

There were no Grade 3 or 4 events related to the study drug. Grade 4 anemia and thrombosis and Grade 3 abnormalities in coagulation assays were related to disease, deep venous thromboses, and anticoagulation, respectively. Myalgias/arthritis due to zoledronate were not seen.

#### Calcitriol Levels

Random calcitriol levels were within the normal range of 15–60 pg/mL. Table 4 shows the peak calcitriol

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**TABLE 3**

<table>
<thead>
<tr>
<th>Type/manifestation</th>
<th>Grade (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td></td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
</tr>
<tr>
<td>PT abnormalities</td>
<td></td>
</tr>
<tr>
<td>PTT abnormalities</td>
<td></td>
</tr>
<tr>
<td>Thrombosis</td>
<td></td>
</tr>
<tr>
<td>Metabolic</td>
<td></td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td></td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td></td>
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<tr>
<td>Hypophosphatemia</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
</tr>
<tr>
<td>Renal/genitourinary</td>
<td></td>
</tr>
<tr>
<td>Dysuria</td>
<td></td>
</tr>
<tr>
<td>Hydronephrosis</td>
<td></td>
</tr>
<tr>
<td>Increased creatinine</td>
<td></td>
</tr>
<tr>
<td>levels</td>
<td></td>
</tr>
<tr>
<td>Nephrolithias</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
</tr>
<tr>
<td>Myalgia (muscle pain)</td>
<td></td>
</tr>
<tr>
<td>Neuropathy</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td></td>
</tr>
<tr>
<td>Bone pain</td>
<td></td>
</tr>
</tbody>
</table>

PT: prothrombin time; PTT: partial prothromboplastin time.
Calcitriol, Zoledronate, and Dexamethasone/Morris et al. 1873

levels of individual patients at Week 5. In addition, the peak calcitriol levels obtained on Day 1 of Week 1 for 2 patients in the 30 μg cohort were 391 pg/mL and 968 pg/mL, respectively.

Markers of Bone Turnover
Changes in BAP and N-telopeptide levels were assessed. Table 5 details the percent changes in these markers. Changes in BAP and N-telopeptide varied and did not appear to be related to calcitriol dose. Zoledronate was associated with a diminution in BAP and N-telopeptide levels, although there was wide interpatient variability.

Antitumor Effects
No patient treated with calcitriol alone or with zoledronate achieved a PSA decrease of ≥ 50%. No patient who received calcitriol alone or with zoledronate exhibited PSA stabilization as a best response. Of the patients who received dexamethasone, 1 patient with castrate testosterone levels experienced a PSA decrease of ≥ 50%, and 1 other patient achieved PSA stabilization on Week 12 of his first treatment cycle. No patient demonstrated a partial response in soft tissue disease.

DISCUSSION
In the current study, we examined the tolerability of high-dose calcitriol alone, with zoledronate, and with dexamethasone. Our data demonstrate that calcitriol can be administered safely at doses up to and including 30 μg orally 3 times per week. All cohorts tolerated treatment well. Three patients had their doses reduced on the basis of laboratory or radiographic criteria. No patient developed clinical evidence of hypercalcemia or nephrolithiasis. The most common Grade 3 adverse event observed in the current study was related to hypophosphatemia, a finding that runs counter to the known physiology of vitamin D. These patients, however, also were receiving zoledronate. The relation between Grade 3/4 hypophosphatemia and zoledronate is well established and accounts at least in part for the observation of this toxicity.

Our safety data agree with the data obtained in previous studies of high-dose pulsed oral calcitriol. Beer et al. administered up to 2.8 μg/kg oral calcitriol per week, and Muindi et al. administered oral calcitriol, escalated to doses of 38 μg 3 times per week, together with paclitaxel. No DLTs were seen in either of those studies. Due to the tolerability of the regimen, an MTD was not defined in the current study. We closed the trial after 3 years of accrual and treatment of > 30 patients. By trial’s end, patients were ingesting 60 tablets of calcitriol 3 times each week, for a weekly administration schedule of 180 tablets (not including dexamethasone). Although we could have defined an MTD if we had continued to escalate doses, we decided that such a treatment schedule was not feasible as a standard outpatient regimen, at least not with this preparation of calcitriol.

The observed tolerability of the regimen may have been related to the poor absorption of the drug, given that such a bolus of pills may not lend itself to uniform absorption. The assessment of serum calcitriol levels was the greatest weakness of the study, because most levels were measured more than 12 hours after patients ingested the drug. At the time of the design and opening of the trial, clinical data regarding high-dose calcitriol were limited to two Phase II studies with primary endpoints defined by changes in PSA. Those studies involved daily calcitriol dosing with intrapatient dose escalations and efficacy endpoints. Later, detailed Phase I pharmacokinetic data became available. Smith et al. examined daily subcutaneous calcitriol administered every other day. Those investi-
gators observed peak concentration within 1–2 hours of administration, with a half-life of 10–17 hours.\textsuperscript{23} Beer et al. then demonstrated that patients who received weekly bolus calcitriol orally exhibited rapid absorption and rapid clearance of the drug, such that peak concentration occurred within the first 8 hours of treatment and then decreased rapidly, with a half-life of 5.6–6.3 hours.\textsuperscript{20} Similarly, Muindi et al. observed peak concentration at 2–5 hours and reported a half-life of 13–25 hours.\textsuperscript{24}

These data indicate that measuring calcitriol levels on the day after administration does not capture peak plasma levels. The majority of patients in the current study (i.e., those who were in cohorts that received calcitriol at doses < 30 µg) received calcitriol before bedtime. When they arrived at the clinic the next day, their levels were likely to have decreased to within normal range. However, when we amended the protocol to capture peak levels, we found that patients achieved peak concentrations that were within the 102–968 pg/mL range. The 30 µg cohort achieved peak plasma levels of 391–968 pg/mL, with a median of 669 pg/mL. Preclinical studies suggest that calcitriol is biologically active in this range. In cultures of prostate carcinoma cell lines, the 50% inhibitory concentration of calcitriol is approximately 1 nM (416 pg/mL).\textsuperscript{13,26}

Muindi et al. performed a detailed pharmacokinetic analysis of calcitriol in combination with paclitaxel and found that the maximum concentration level (C\textsubscript{max}) for the 22 g per day cohort was 460 pg/mL, whereas C\textsubscript{max} for the 29 g per day cohort was 710 pg/mL.\textsuperscript{24} These were similar to our findings regarding peak concentration levels. Although it is possible that paclitaxel influenced the metabolism of calcitriol in the study conducted by Muindi et al., no such influence was present in a study involving docetaxel and calcitriol.\textsuperscript{27} Beer et al.\textsuperscript{20} reported peak levels as high as 1635 pg/mL at a dose of 0.48 µg/kg per week (33 µg per week). Above this dose, plasma levels did not increase linearly, and there was considerable interpatient variability. Although both studies used the same preparation, our peak plasma levels were lower than those reported by Beer et al., who used a more rigorous schedule of pharmacokinetic analysis compared with our study. This may account in part for the more accurate identification of the true peak level. Otherwise, the reason why the peak levels reported by Beer et al. and Muindi et al. were higher than the levels reported in the current study is not known.

One patient in the current study experienced a decrease in PSA levels of ≥ 50%, and 1 patient experienced PSA stabilization. Both received dexamethasone, and antitumor effects have been observed in studies using steroids alone to treat prostate carcinoma.\textsuperscript{28,29} The other patients participating in the study experienced progression. The current study was a Phase I trial and was not designed to test efficacy, but preliminary efficacy results reflected those of other studies. No study of calcitriol monotherapy has demonstrated posttreatment PSA declines of ≥ 50%. One Phase II study in which daily oral dosing was used found that 2 of 14 patients achieved PSA decreases of 25% and 45%, respectively.\textsuperscript{17} Another study in which daily oral dosing was used found that the rate of increase in PSA levels was attenuated in six of seven patients. In that study, the PSA doubling time increased by 47%, an endpoint that has not been shown to translate into clinical benefit, and that exhibited significance in only 1 of 2 statistical analyses performed.\textsuperscript{18}

In this context, our data were not compelling enough for us to pursue Phase II studies using calcitriol as a single agent. In combination with other drugs, however, calcitriol may be promising. A Phase II trial of calcitriol and docetaxel demonstrated that 89% of patients experienced a PSA decrease of > 50%, with a 53% response rate for patients with soft tissue tumors. These rates are higher than what might be expected historically from docetaxel alone.\textsuperscript{27} Additional studies of this combination regimen currently are underway.

In summary, pulsed calcitriol was well tolerated at doses up to and including 30 µg per day administered 3 times per week in combination with zoledronate. The peak plasma levels of patients in the 24 µg and 30 µg cohorts corresponded to levels that were biologically active in preclinical studies. Because patients were required to ingest 180 tablets per week using this preparation, we will not pursue Phase II studies to formally assess the efficacy of this regimen.

REFERENCES


