Phase II Study of 1α-Hydroxyvitamin D2 in the Treatment of Advanced Androgen-independent Prostate Cancer

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ABSTRACT

Purpose: In this single institution Phase II trial, we evaluated the efficacy of the vitamin D analogue, 1α-OH-D2, in patients with advanced hormone-refractory prostate cancer.

Experimental Design: The patients initially received 1α-OH-D2 at 12.5 μg p.o. every day, which was dose adjusted for hypercalcemia. Given the cytostatic nature of the drug, the primary study end point was progression-free survival for a minimum of 6 months. The secondary end point was further characterization of drug toxicity.

Results: A total of 26 patients was enrolled. Using the intent-to-treat population, stable disease was seen for an average of 19.2 weeks (median 12 weeks, range 3–108 weeks). Twenty patients were evaluable for response. The one patient that achieved disease stabilization for >2 years elected to come off-study because of patient preference. His last disease evaluation showed no evidence of progression.

No objective responses were seen. Previous and ongoing clinical observations strongly imply that PSA could be a misleading surrogate marker for clinical effect with this type of drug. Therefore, prostate-specific antigen was not used as a marker for disease response. Toxicity was as expected with mild hypercalcemia and associated symptoms like constipation and prerenal azotemia seen in some patients. Six (30%) evaluable patients experienced stable disease for >6 months, suggesting possible cytostatic activity.

Conclusion: The results of this and other trials suggest further clinical investigation in this disease with vitamin D analogues alone or in combination with other agents, such as chemotherapy, should be pursued.

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INTRODUCTION

Prostate cancer is the most common malignancy among males in the United States with an estimated 189,000 new cases and 30,200 deaths for the year 2002 alone (1). Although androgen ablation is the standard initial therapy for metastatic prostate cancer, nearly all these patients will eventually develop androgen-independent disease after a median of 18–24 months of hormonal therapy. The current standard is to then discontinue the antiandrogen in hopes that a withdrawal effect will be observed. Although possible, this effect occurs in <15% of patients and usually is not durable in response (2). Despite palliative benefit, no chemotherapeutic regimen has been proven to significantly improve overall survival in these advanced hormone-refractory patients, with survival remaining relatively short (median 12 months). Thus, newer agents for the management of androgen-independent prostate cancer are needed.

In 1990, it was hypothesized that vitamin D deficiency could be a risk factor for prostate cancer as age, African-American race, and residence in a northern latitudes were not only associated with an increased incidence of prostate cancer but also a relative decrease in the levels of the vitamin (3). It was thought that vitamin D could maintain the differentiated phenotype of prostatic cells, and in the presence of low levels of vitamin D, subclinical prostate cancer may progress to clinical disease. This hypothesis was supported by two separate retrospective analyses measuring vitamin D levels from stored sera and showing that mean calcitriol levels were lower in patients who later developed prostate cancer compared with age-matched controls (4, 5).

Because vitamin D has well-defined roles in calcium and phosphate homeostasis, it is of no surprise that VDRs have been found in the bone, intestine, kidney, and parathyroid gland. We now know that VDRs are found in a wide variety of other cells and that this seco-steroid hormone can regulate the growth and maturation of these various tissues. In vitro cultures of prostate cancer cell lines with physiological levels of calcitriol inhibited proliferation of LNCaP and PC3 but not DU145. Calcitriol also caused a dose-dependent stimulation of PSA production in LNCaP cells, suggesting that vitamin D was both antiproliferating and differentiating in prostate cancer cells (6).

Early clinical trials using oral calcitriol in prostate (7) and hematological malignancies (8) were conducted but yielded negative results. Presumably, inadequate doses of calcitriol were able to be administered secondary to complications from hypercalcemia. Later, a small pilot study in patients with biochemical...
failure after radical prostatectomy or radiation therapy did show evidence in prolongation of the PSA doubling time using calcitriol in the select patients studied (9). Because the chemotherapeutic benefit of calcitriol was difficult to exploit because of hypercalcemic side effects, less hypercalcemic vitamin D analogs have been developed for clinical testing. Some biological effects have already been observed in colon (10, 11), bone (12), and breast cancer cell lines (13). Many of these have also shown similar or increased activity compared with calcitriol in inhibiting prostate cancer growth in vitro, with markedly decreased effects with regards to hypercalcemia development. These studies confirmed that the inhibitory growth properties of vitamin D can be enhanced with analogues, as long as the binding affinity for the VDR is retained (14–16). One such analogue of interest is 1α-OH-D2.

We have completed previously and published a Phase I study using 1α-OH-D2 in patients with HRPC (17). This p.o. drug was administered with doses ranging from 5 to 15 μg every day. Main toxicities were hypercalcemia with associated secondary serum creatinine increases. A total of 21 evaluable patients was treated. Two patients achieved a PR, whereas 5 others maintained SD for > 6 months. Given the promising results, this Phase II trial using 1α-OH-D2 was conducted in advanced HRPC starting at the recommended dose of 12.5 μg/day given continuously.

MATERIALS AND METHODS

Patient Selection. Patients were considered eligible if they had advanced androgen-independent prostate cancer that progressed after androgen withdrawal. Patients had to have histologically proven disease with progressive soft tissue or bony metastasis. If the patients did not have measurable disease but had bone scan abnormalities, a serum PSA > 10 ng/ml was required. All patients had to show a progressively rising PSA ≥ 2 weeks apart and ≥ 50% increase over the baseline values obtained during hormonal interventions. PSA abnormalities alone were not considered evaluable, and those patients were excluded from this trial. Patients were eligible if they had an Eastern Cooperative Oncology Group performance status of 0–2; adequate bone marrow function with absolute neutrophil count ≥ 1200/μL, hemoglobin ≥ 8 grams/dl, and platelets ≥ 100,000/μL; stable renal function with creatinine ≤ 1.8 mg/dl, adequate hepatic reserve with normal bilirubin, and aspartate aminotransferase ≤ 2.5 times the upper limit of normal. A corrected serum calcium ≤ 10.2 mg/dl was required at study entry. Patients were excluded if they had received more than two previous cytotoxic chemotherapy regimens (or chemotherapy within 4 weeks of beginning study), had received strontium in the past, or had any history of brain metastasis. Any history of idiopathic urinary calcium stone disease, chronic hypercalcemia, or gastrointestinal malabsorptive conditions was also prohibited. Lastly, any use of digitals, thiazide diuretics, or calcium supplementation was not allowed. Patients who did not have an orchietomy were continued on their luteinizing hormone-releasing hormone during the study, although the androgen was discontinued. Uncontrolled infections or other serious intercurrent medical illnesses were not allowed. All patients gave written informed consent in compliance with state, federal, and institutional guidelines.

Study Plan. At study entry, all patients underwent a complete history and physical exam, including a complete blood count, serum chemistries, and disease assessment (bone scan, CT imaging, and PSA). Baseline vitamin D metabolites, 24-h urine calcium levels, as well as other investigational laboratories were obtained as well. Eligible patients were given 12.5 μg of 1α-OH-D2 (five each of 2.5 μg capsules) continuous once a day p.o. before their a.m. meals. This dose is based on the recommended Phase II dose from the completed Phase I trial. 1α-OH-D2 was provided by Bone Care International (Madison, WI) in soft, gelatinized capsules in units of 2.5 μg/capsule. Inactive ingredients in order of decreasing weight included: fractionated coconut oil, gelatin, glycerin, titanium dioxide, D&C yellow no. 10, ethanol, and butylated hydroxyanisole.

Weekly toxicity assessments, vital signs, calcium, phosphorus, and albumin levels were obtained during the first 4 weeks of drug administration. Thereafter, physical examinations, complete blood counts, serum chemistries, vitamin D metabolite levels, 24-h urine calcium, and PSA levels were evaluated every 4 weeks while the patient was on study. Radiographic disease assessments were repeated every 12 weeks or sooner if clinically indicated.

Toxicity and Dose Modifications. Patients with any grade 1–2 toxicity (defined by the National Cancer Institute common toxicity criteria) were allowed to continue on treatment without dose modification. However, any grade ≥ 3 toxicity (excluding anemia and alopecia) felt related to drug required holding drug until the toxicity resolved to ≤ 2. The drug was then resumed at a dose one capsule (2.5 μg) lower. If the toxicity did not improve to grade ≤ 2 within 14 days of stopping the drug, that patient was removed from the study. Patients with grade ≥ 1 hypercalcemia (corrected for serum albumin) or grade ≥ 2 creatinine elevation had their drug held, then resumed at one capsule (2.5 μg) lower once toxicity resolved.

Response Criteria. Because of the presumed slow onset of any potential benefit, we elected to only use patients who completed ≥ 8 weeks of therapy in the determination of potential usefulness of this cytostatic agent. Therefore, only patients completing ≥ 8 weeks of therapy were considered evaluable for response. Evidence of progression after 8 weeks was considered a treatment failure. Changes in performance status, PSA, and weight were noted but not used as response criteria. For this study, a complete response was defined as disappearance of all known disease during two observations at least 4 weeks apart, during which no new lesions develop. For patients with bone only disease, normalization of the bone scan was required. A PR was defined as ≥ 50% decrease in the sum of the products of the perpendicular tumor diameters of all measurable disease documented for ≥ 4 weeks. No new lesions or increased size of any existing lesion was allowed. For patients with bone only disease, a PR required a ≥ 50% decrease in the number of bone scan lesions. Progressive disease included any unequivocal increase ≥ 25% in the size of any existing lesion or the appearance of any new lesion. SD was any other condition not met by the criteria outlined in complete response, PR, or progression.

Correlative Studies. Blood samples were collected at baseline and throughout the treatment period and stored at
patients had measurable disease. See Table 1 for patient characteristics.

Objective Response. Of all 26 patients enrolled, 6 patients failed to complete ≥8 weeks of therapy and were therefore not evaluable for response. One of those patients had visceral as well as bony metastasis and progressed by week 7 with a worsening perirectal mass. Another had liver and bony metastasis and was removed from the study at week 5 for clinical progression (worsening pain), despite stable bone scan. Two patients progressed clinically with new lesions on their bone scan, one at week 5 and the other by week 6. Another patient was removed at week 4 after developing pneumonia. He was then found to have a secondary malignancy with a stage IIIA squamous cell lung cancer. The last patient had to be removed from study at week 3 for development of drug toxicity (see Toxicity). Of the remaining 20 (evaluable) patients, no objective responses were seen despite 8 patients having measurable disease. One of those patients had biopsy confirmed pulmonary metastases and mediastinal lymphadenopathy at enrollment and had maintained SD since July 2000 (>2 years). He recently chose to discontinue drug after 108 weeks of therapy given that he now resides out of state and when last seen had a second episode of a grade 1 hypercalcemia despite remaining at the lowest dose of 1α-OH-D_2 allowed. His CT, bone scans, and PSA remain stable. All but two patients had radiographic evidence for disease progression. Those two patients had clinical deterioration with increased bony pain. In total, 6 evaluable patients did achieve SD for >6 months meeting our initial criteria for drug activity.

PSA Response. PSA response was not considered a surrogate marker in this study given in vitro data, indicating stimulation of PSA production with vitamin D analogues. We observed all but 2 patients with a continual rise in PSA while on therapy (figure not shown). Of interest, one of the patients with a PSA decline had a baseline PSA of 44.7 ng/ml, and this dropped from the start to a nadir of 29.6 ng/ml at week 12. He had evaluable lymphadenopathy as well as bone scan positivity from the beginning and eventually progressed by bone scan only at week 44 with an associated PSA of 74.7 ng/ml. The other patient started with a PSA of 23.4 ng/ml, and his PSA reached nadir at week 8 to a PSA of 6.7 ng/ml. Although his PSA never did rise again above baseline, he was removed from the study at week 28 secondary to clinical progression with increased bony pain. His PSA at that time was only 20 ng/ml.

Toxicity. A total of >448 weeks of drug was administered during this study. Of the 26 total patients, all but 6 completed ≥8 weeks of therapy. As expected, common toxici-

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient characteristics</th>
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<tr>
<td>Number of patients</td>
<td>26</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>70 (range 57–85)</td>
</tr>
<tr>
<td>Performance status (Eastern Cooperative Oncology Group)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>1</td>
<td>19</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Previous cytotoxic therapy</td>
<td>5 (19%)</td>
</tr>
<tr>
<td>Previous palliative radiation</td>
<td>9 (35%)</td>
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<table>
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<th>Sites of disease</th>
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<tr>
<td>Bone</td>
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<tr>
<td>Lymph nodes</td>
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<tr>
<td>Lung</td>
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<th>Table 2</th>
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<tr>
<td>Dose</td>
<td>Hypercalcemia (grade)</td>
</tr>
<tr>
<td>No. of courses</td>
<td>1</td>
</tr>
<tr>
<td>12.5 μg</td>
<td>46</td>
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<tr>
<td>10.0 μg</td>
<td>19</td>
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<tr>
<td>7.5 μg</td>
<td>14</td>
</tr>
<tr>
<td>5.0 μg</td>
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−70°C in the University of Wisconsin Analytical Laboratory. Serum levels of osteocalcin, bone-specific alkaline phosphatase, and N-telopeptide were assayed by Pacific Biometrics, Inc. (Seattle, WA). Additional samples were collected in 7-ml EDTA tubes using 19 or 21 gauge needles to minimize hemolysis. These samples were immediately stored at 4°C until centrifugation when the top 1 ml of plasma was isolated and frozen at 70°C in NUNC tubes. These samples were later analyzed for TGFβ_3 using a 96-well plate quantitative sandwich immunoassay (Quantikine human TGFβ_3; R&D System, Minneapolis, MN). The buffy coat was also collected and frozen for future analysis of T-cell receptor-associated ξ chain expression.

Statistical Analysis. This study was planned using a two-stage design. At the time of the protocol development, the published median survival for patients with advanced HRPC was ~12 months. Therefore, most patients should develop evidence of radiographic disease progression well before that median survival is reached. Given the cytostatic nature of the 1α-OH-D_2, we chose to use PFS at 6 months as the primary outcome measure. We assumed that if ≥30% of the patients maintained freedom from progression for 6 months, this therapy would be of clinical interest. Initially, 20 evaluable patients would be enrolled in the first phase of the trial. These patients would then be followed for 6 months with the assumption that if <5 of the first 20 patients maintained PFS for 6 months, the trial would be terminated and declared negative. Otherwise, an additional 20 patients (40 patients maximum) would be enrolled in a second phase of the trial. Time to progression was computed from the first day of drug.

RESULTS

Patient Characteristics. From January 1999 to October 2000, a total of 26 patients was enrolled in this trial, all at the University of Wisconsin Comprehensive Cancer Center. The median age was 70 years (range, 57–85 years), and the median performance status was 1 (range, Eastern Cooperative Oncology Group performance status 0–1). All patients had stage D2 disease (CT or bone scan positive) with rising PSA before enrollment. Patients needed to be on stable doses of luteinizing hormone-releasing hormone agonist or have had a previous orchectomy. Five patients received previous chemotherapy, two of which had two different chemotherapy regimens. Nine patients received previous palliative radiation therapy. Twelve
ties included hypercalcemia (grade 1) with occasional resultant effects like a transient elevated creatinine level (Table 2) or constipation. Few patients had nausea, abdominal discomfort and bloating, fatigue, or anorexia. Individual patients complained of hot flashes, diarrhea, or weakness. Two patients developed grade 1 aspartate aminotransferase elevation at the time of their disease progression. This was felt possible related to the study drug but more likely attributable to progressive bony metastasis. One patient at the 12.5 µg/day dose did develop grade 3 hypophosphatemia (phosphate 2 mg/dl) with a concurrent grade 1 corrected calcium (Ca^2+ 10.32 mg/dl) at day 29 of therapy. His drug was held with normalization of both his calcium and phosphorus level within 1 week, and he was restarted on drug at the next lower dose level. See Table 3 for frequent adverse events. Only one patient was withdrawn for an adverse drug effect (grade 3 hypercalcemia, grade 2 creatinine, and grade 2 dehydration). This patient was receiving 12.5 µg of 1α-OH-D₂ and developed hypercalcemia only after 1 week of drug. He was removed from the study with concerns of rapidly progressive cancer and persistent grade 1 hypercalcemia and grade 2 dehydration after 2 weeks of holding drug. Of the 26 patients, only 8 patients received 8 weeks of therapy at 12.5 µg/day. Dose reductions were eventually performed on 16 of the 26 patients with final doses ranging from 5 to 12.5 µg/day, median 10 µg/day (five patients were reduced to 10 µg/day, nine patients to 7.5 µg/day, and two patients to 5 µg/day). No patients died while on this study.

**Correlative Studies.** TGFβ₁ levels were determined at time of enrollment and then every 4 weeks while the patient remained on protocol. The mean baseline level of TGFβ₁ in our advanced hormone-refractory prostate cancer population was 4.41 ng/ml (SD 2.88). The mean levels appeared to increase over baseline in subsequent determinations as shown in Fig. 1. Various markers of bone turnover (osteocalcin, N-telopeptide, and bone-specific alkaline phosphatase) were analyzed using the same time points. As reported previously (17), the large inter and intrapatient variability made interpretation of the measured values difficult, and no specific trends relative to baseline values [bone-specific alkaline phosphatase: mean 76.9 units/liter, range 15.3–274.5 units/liter; osteocalcin: mean 39.3 ng/ml, range 10.6–90.8 ng/ml; N-telopeptide: mean 21 nmol bone collagen equivalent, range 6.4–38.1 nmol bone collagen equivalent] could be made when looking at mean values. To normalize for the interpatient variability, measured values were adjusted relative to the baseline values and plotted against time. Again, no significant trend could be established when looking at N-telopeptide and bone-specific alkaline phosphatase levels. There was a slight increase in osteocalcin levels as shown in Fig. 2.

**Time to Progression and Survival.** The mean time to progression in the intent-to-treat population was 19.2 weeks (median 12 weeks, range 3–108 weeks). When considering only the evaluable patients, the mean time to progression was 23.4 weeks (median 12 weeks, range 8–108 weeks).

As of August 21, 2002, 16 patients had expired. Using an intent-to-treat analysis, the median survival as computed by the Kaplan-Meier method was 487 days with a 95% CI of (381, infinity). Considering only evaluable patients (those receiving at

| Table 3 | Adverse event (% of patients) |
|-----------------|-----------------|-----------------|-----------------|
| Adverse event   | Grade 1 | Grade 2 | Grade 3 |
| Constipation    | 9 (35%) |          |        |
| Abdominal discomfort | 2 (8%) |          |        |
| Nausea          | 2 (8%)  | 1 (4%)  |        |
| Fatigue         | 2 (8%)  | 1 (4%)  |        |
| Anorexia        | 2 (8%)  |          |        |
| Dehydration     | 1 (4%)  |          |        |
| Hot flashes     | 1 (4%)  |          |        |
| Weakness        | 1 (4%)  |          |        |
| Diarrhea        | 1 (4%)  |          |        |
| Rash            | 1 (4%)  |          |        |
| Transaminase elevation | 2 (8%) |          |        |
| Phosphatemia (hyper/hypo) | 1 (4%) | 1 (4%) |        |

**Fig. 1** Measurement of plasma TGFβ₁ levels at baseline and after every 4 weeks of 1α-OH-D₂. Mean plasma levels of TGFβ₁ were observed to increase over baseline.

**Fig. 2** Measured osteocalcin level at baseline and after every 4 weeks of 1α-OH-D₂ therapy. Results shown as a ratio of measured values over baseline osteocalcin levels plotted against time in weeks to minimize interpatient variability.
least 8 weeks of drug), we chose to calculate the baseline survival starting at 8 weeks beyond treatment onset to minimize the bias of selecting patients on the basis of their future outcome. Using this method, the actuarial median post-first-course survival was 630 days with a 95% CI of (381, infinity). These survival curves are shown in Figs. 3 and 4.

**DISCUSSION**

The treatment of prostate cancer has been continuously refined as new information regarding the role of prostatectomy (18), the timing of hormone administration (19, 20), and use of chemotherapy (21) are studied. Although some improvements in prostate cancer-related mortality have been observed, most of this is likely related to better management of treatment and disease-related morbidity, rather than actual impact on the disease itself. Unfortunately, >30,000 patients are estimated to die each year because of prostate cancer, and many more are debilitated from advanced disease. It is clear that new therapies are needed.

Vitamin D is a secosteroid that has shown extensive laboratory and clinical evidence that it may be useful in the treatment or prevention of prostate cancer. Because early trials with calcitriol resulted in dose-limiting hypercalcemia, we have focused instead on vitamin D analogues to maximize dose intensity. Despite more current data suggesting safety of pulse-dose calcitriol, we have continued to pursue these analogues with the assumption that more chronic administration of these cytostatic agents are necessary to optimally maintain the antiproliferative and differentiating effects of this class of drug. During Phase I evaluation of 1α-OH-D$_2$, two patients at dose levels of 5 and 7.5 μg/day had radiographically confirmed PRs, indicating drug activity in patients with prostate cancer. Toxicity was limited to hypercalcemia and secondary reversible increases in serum creatinine with a recommended Phase II dose of 12.5 μg/day (17). This Phase II trial was conducted to better define the drug toxicity and activity in patients with advanced hormone-refractory prostate cancer.

Overall, we did not observe any unexpected drug toxicity. Mild, clinically insignificant hypercalcemia was frequently seen and easily controlled with either dose modifications or brief cessation of therapy. Because of the toxicity (one grade 2 and one grade 3 serum creatinine increase) observed in our Phase I trial, we proceeded cautiously and had a low threshold for dose reductions. One may argue that we were too conservative given that the majority of the hypercalcemia seen in this trial was only grade one, but our previous experience showed that a few of these patients could develop more clinically significant hypercalcemia with continued therapy. In any event, dose intensity was likely not fully maximized (50% of evaluable patients eventually dose reduced), and many patients were probably dose reduced for clinically insignificant hypercalcemia. The dose modification schema made assessment of drug activity difficult to generalize as each patient eventually received various doses of 1α-OH-D$_2$.

We did meet our first study end point during this study as 6 of 20 evaluable patients did achieve PFS for >6 months on therapy. As mentioned previously, the statistical basis for this decision was the assumption that the median survival in patients with advanced hormone-refractory prostate cancer was 12 months. As we neared the closure of the first stage in this trial, other trials began reporting more recent median survival data approaching 18 and 20 months (22). Thus, we decided not to proceed to the second phase of the protocol (enrollment of an additional 20 patients) because the more recent survival data implied that our initial statistical parameter was too low and that investing more patients was not going to allow us to develop any clinically relevant response information. In any event, we were encouraged that six patients did achieve disease stabilization for
>6 months. This included one patient who remains stable for over 2 years and counting. What is interesting is that our survival data are similar to those reported in these recent trials with median survival of 16 months in the intent to treat population. We questioned whether our median survival was inflated given the fact that our patients were carefully selected to exclude those requiring urgent chemotherapy and thus not good candidates for this cytostatic agent. Because individual trials use different exclusion criteria or contain various levels of patient acuity, generalizing survival results has to be made with much reservation. To allow some inter-trial comparison, we used the nomogram developed by Kattan et al. (Memorial Sloan-Kettering) that predicts median survival of patients with progressive prostate cancer after castration using baseline screening laboratories and clinical parameters (23). Using the nomogram, our predicted median survival would be 16.3 months for the intent-to-treat population. This is very similar to our observed median survival of 16 months. Using the nomogram for the evaluable patients, our predicted median survival would be 17.7 months (compared with the observed median survival of 21 months). We have questioned whether a more pronounced response could have been observed had we been more aggressive in maintaining dose intensity. Dose intensity could have been maintained either by allowing grade 1 hypercalcemia and/or not dose reducing after resolution of grade 1 or 2 hypercalcemia.

TGFβs are multifunctional growth factors that have been associated with both protumorigenic as well as tumor-inhibitory properties (24). Interestingly, vitamin D and TGFβ may share identical actions on the cell’s growth and differentiation because TGFβ has been observed to inhibit proliferation of epithelial cells. It has been demonstrated that the inhibitory effect of calcitriol on cell growth could in fact be related to an induction of TGFβ synthesis in a paracrine/autocrine loop (25). We did observe increasing mean TGFβ levels over baseline during this trial. Whether this increase is secondary to disease progression or evidence of drug activity is unknown. Theoretically, because TGFβ has downstream effects on cell growth, it is conceivable that its level may rise early because of the inducing effect of the vitamin D analogue, before later decreasing because of tumor regression. Because no objective tumor responses were seen in this trial, no additional inferences could be made.

As reported previously, it is difficult to correlate drug activity using the markers for bone turnover in this patient population (19). Presumably, the presence and amount of osteoblastic metastasis will influence the levels of osteocalcin, N-telopeptide, and/or bone-specific alkaline phosphatase measured. Data confirming doxercalciferol absorption (reflected by measured metabolite levels) and pharmacodynamics were described previously in our Phase I trial (17) and do confirm the physiological presence of active drug in all patients.

Lastly, the observed increase in PSA can raise some questions to whether the increase is simply attributable to disease progression versus the differentiating effects of the treatment. Understandably, the increase in PSA while on therapy can be difficult to ignore, not only for the patient, but also for the treating physician. Although the use of PSA as a marker for disease response has been validated by the Prostate-Specific Antigen Working Group as a reasonable method to evaluate outcomes in Phase II clinical trials (26), they do acknowledge that some newer, noncytotoxic agents may modulate PSA expression independent of their effects on cell growth, and therefore, the use of PSA as a surrogate marker in these cases has not yet been validated. Although rising PSA is of concern, given the preclinical data and early clinical data showing rising PSA despite tumor response, this trial relied on other accepted “surrogate markers” like CT scans and bone scans to assess disease progression.

In conclusion, from our Phase I and II trials of 1α-OH-D₂ in patients with advanced HRPC, we have shown evidence of drug
activity that warrants further investigation. Although the Phase II trial did not have any objective responses, we did observe disease stability >6 months in 30% of the patients. For a cytostatic drug, this is encouraging, especially because the treatment involves a fairly nontoxic, p.o. medication. We are also encouraged by the observed median survival of 630 days (21 months) in the evaluable patients, which is higher than the 17.7 months predicted by the survival nomogram for that patient group. Admittedly, we did not have a control arm for this Phase II trial so any implication on improvement in overall survival cannot be made.

We are currently looking at the effects of 1α-OH-D2 on both normal prostate cells and prostate carcinoma cells by matching prostate biopsies with subsequent 1α-OH-D2-treated prostatectomy specimens. Hopefully, the mechanism and effect of vitamin D can be further elucidated. In addition, there is presumably synergistic activity with vitamin D and chemother-apy (27) because of different mechanisms of action, and we are currently examining this issue clinically. Lastly, the use of these vitamin D analogues can be combined with bisphosphonates to maximize dose intensity and further exploit different mechanisms of action, especially in a disease prone to bony metastasis like prostate cancer. What is clear is that additional trials involving vitamin D and its analogues are needed.

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