Phase I/II Study of 19-nor-1α-25-Dihydroxyvitamin D2 (Paricalcitol) in Advanced, Androgen-Insensitive Prostate Cancer

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Abstract Purpose: We assessed the safety and efficacy of the vitamin D analogue, 19-nor-1α-25-dihydroxyvitamin D2 (paricalcitol), in patients with androgen-independent prostate cancer. Experimental Design: Patients received paricalcitol i.v. three times per week on an escalating dose of 5 to 25 μg (3-15 μg/m2). The primary end point was prostate-specific antigen (PSA) response. Secondary end points were characterization of toxicity in this population, changes in serum parathyroid hormone (PTH), and survival. Results: A total of 18 patients were enrolled. No patient showed a sustained 50% drop in serum PSA, despite several large declines in PSA (e.g., 1,300 ng/mL). Paricalcitol was well tolerated. One instance of significant hypercalcemia, a serum calcium of 14.3 mg/dL, was observed at the highest dose (25 μg). At entry into the study, seven (41%) of the patients had elevated serum levels of PTH, which were significantly reduced by paricalcitol. Higher levels of serum PTH at study entry were significantly and negatively associated with survival (P < 0.01). Conclusion: No objective responses were seen in the primary end point. However, elevated serum levels of PTH, a common feature of advanced prostate cancer, were reduced by paricalcitol. Because elevated PTH is associated with increased cardiovascular and skeletal morbidity, including an increased risk for pathologic fracture, further evaluation of paricalcitol in the reduction of skeletal morbidity in advanced prostate cancer is warranted.

Prostate cancer is the most prevalent (nonskin) cancer among American men and the second most fatal, accounting for >30,000 deaths in 2005 (1). For men with advanced disease, the mainstay of prostate cancer therapy is androgen withdrawal. Although androgen withdrawal is usually effective in lowering prostate-specific antigen (PSA) in men with prostate cancer, in men with metastatic disease, the duration of response is brief (about 14-18 months), and androgen-independent prostate cancer (AIPC) supervenes in virtually all treated men. The median survival once AIPC develops is 12 to 18 months. Although recent clinical trials in AIPC have shown a survival benefit for docetaxel-based chemotherapy, the benefit is modest (about 2 months; refs. 2, 3). Thus, new therapies for AIPC are urgently needed (4, 5).

Considerable attention has focused on the role of vitamin D in prostate cancer, stemming from the observation by Schwartz and Hanchette that mortality rates from prostate cancer are inversely related to levels of UV radiation, the major source of vitamin D (6). Vitamin D is synthesized in response to sunlight and undergoes hydroxylation in the liver to 25-hydroxyvitamin D (calcidiol) and then in the kidney to form 1,25-dihydroxyvitamin D (calcitriol), the hormonal form of vitamin D. Extensive research has shown that prostate cells, including prostate cancer cells, express specific receptors (VDR) for 1,25-dihydroxyvitamin D. When bound to the VDR, 1,25-dihydroxyvitamin D regulates >60 genes that exert prodifferentiating, antiproliferative and antimetastatic effects on prostate cells, including effects on cell cycle. These data support the use of calcitriol and analogues as therapeutic agents in prostate cancer (see refs. 7, 8 for reviews).

Promising preclinical evaluations of calcitriol and analogues have appeared in prostate cancer animal models (9, 10). Several clinical trials of calcitriol and analogues in AIPC have been reported, including those using calcitriol (11, 12) and the prodrug, 1α-hydroxyvitamin D2 (doxercalciferol) as monotherapy (13), as well as calcitriol in combination with other agents (e.g., docetaxel, zoledronate, and dexamethasone; ref. 14). Recently, Beer et al. reported an 81% response rate for the combination of calcitriol and docetaxel in metastatic prostate cancer versus an expected response of 40% to 50% for docetaxel alone (15).

The principal toxicity of calcitriol as an anticancer drug is hypercalcemia. The calcitriol analogue, 19-nor-1α-25-dihydroxyvitamin D2 (paricalcitol, Zemplar), was approved by the Food and Drug Administration in 1998 for the prevention and treatment of secondary hyperparathyroidism associated with chronic renal failure. In patients with chronic renal failure,
paricalcitol is three to four times less calcemic than 1,25-dihydroxyvitamin D (see ref. 16 for a review). We recently reported that paricalcitol was as effective as 1,25-dihydroxyvitamin D in transactivating the prostastic VDR and in inhibiting the growth of prostate cancer cell lines and primary cultures of prostate cancer cells in vitro (17). These findings served as the basis for the exploration of paricalcitol in AIPC.

Materials and Methods

Eligibility criteria. Eligible patients for this phase I/II trial were men with confirmed adenocarcinoma of the prostate, advanced, androgen-insensitive disease; an Eastern Cooperative Oncology Group performance status of 1 to 2; and a PSA > 10 ng/mL. This was a dose escalation trial, with paricalcitol doses starting at 5.0 μg (3.0 μg/m²) i.v. thrice per week and escalating at 5.0-μg intervals to 25.0 μg (15.0 μg/m²). The protocol was approved by the Institutional Review Board at Wake Forest University, and all patients signed informed consent forms before registration.

Toxicity was assessed after 4 weeks. If no grade 4 toxicities were observed, treatment continued for up to 12 weeks. At this time, if disease was stable or there was a PSA response, the patient continued on the same dose. If a patient progressed, the dose was escalated to the next higher level. Dose escalation was not allowed until resolution of any grade 3 toxicity. No more than one dose escalation was permitted per patient.

Drug formulation. Paricalcitol (paricalcitol injection) is a calcitriol analogue whose chemical designation is 19-nor-1a,3b,25-trihydroxy-9,10-secoergosta-5(11b),7(22),24(28)-trien-3α-ol. It is available as a sterile, aqueous solution for i.v. injection and was provided courtesy Abbott Laboratories (Abbott Park, IL).

Serology. Pretreatment serum levels of 25-hydroxyvitamin D (a measure of vitamin D sufficiency) were determined at study entry. Measurements of serum calcium, phosphorus, and creatinine were obtained after 2 weeks of treatment. Serum calcium, phosphorus, and PSA were measured after 4, 8, and 12 weeks. Serum parathyroid hormone (PTH) was measured at baseline and after 12 weeks. Serum alkaline phosphatase and the calcium-phosphorus (Ca × P) product, corrected for serum albumin, was obtained at baseline and after 12 weeks of treatment.

Serum calcium and phosphorus was measured with the ADVIA 1650 system. The measurements of phosphorus are based on Daly and Ertinghausen procedure, which relies upon the formation of a UV-absorbing complex between phosphorus and molybdate. The calcium method is based on the work of Gitelman, in which calcium ions form a violet complex in an alkaline medium. Measurement of intact PTH employed the immunometric assay and used the Immulite Analyzer. PSA was measured using the Bayer Immuno 1 System, using a sandwich immunoassay. 25-Hydroxyvitamin D was measured by RIA.

Outcome assessment. The primary outcome was PSA response, defined as a 50% decrease in PSA with confirmatory consecutive measurement at least 4 weeks apart. PSA was assessed monthly. Secondary outcomes were changes in intact PTH, evaluation of hypercalcemia, Ca × P product, other toxicities, and survival. Progression was defined as a 50% increase in serum PSA or the appearance of a new metastatic lesion at any site.

Statistical considerations. The phase I/II study was designed as a dose escalation study to determine the maximally tolerated dose of paricalcitol in these patients. Three patients were to be treated initially at each of the first two dose levels, which approximate the initial dose of paricalcitol used in the treatment of patients with secondary hyperparathyroid disease. Accrual of an additional three patients to a given dose level was planned if one of three patients at that dose level experienced a grade 4 toxicity. Six patients were to be treated at each of the last three dose levels to explore doses closer to, and beyond, the maximal doses previously reported.

If two or more patients on a given dose level experienced a grade 4 toxicity, the study would be stopped. If the true probability of a dose-limiting toxicity at one of the first two dose levels was 50% or 70%, the probability of stopping at that dose was 83% or 97%, respectively. If the true probability of a dose-limiting toxicity at one of the last three dose levels was 50% or 70%, the probability of stopping at that dose was 89% or 99%, respectively. Survival analysis employed an intent-to-treat basis using the Kaplan-Meier method.

Results

Patient characteristics. Eighteen men were recruited between January 2001 and May 2002. Pretreatment characteristics of the patients are shown in Table 1.

Prior therapies. Three patients were treated initially with prostatectomy; six were treated with primary radiation therapy. Fifteen patients were treated with various forms of hormonal therapy, including luteolide, bicalutamide, flutamide, nilutamide, and ketoconazole/prednisone. Six patients had been treated with orchietomy. Five patients received prior treatment with chemotherapy (either single-agent doxorubicin or combination therapy with vineralbine tartrate, doxorubicin, and prednisone). All but two patients had received more than one type of prior therapy, and most men had been treated with multiple therapies. No patient had received prior therapy with bisphosphonates.

Toxicity. Eleven patients were dose escalated, for a total of 29 cycles delivered. Intravenous paricalcitol was well tolerated. In general, adverse side effects were mild and/or minimal. Mild nausea was reported by eight patients. Vomiting was noted by two patients and was also mild. One patient

Table 1. Summary of patient characteristics at enrollment

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>18</td>
</tr>
<tr>
<td>Age (y), median (range)</td>
<td>74.4 (51-83)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>17</td>
</tr>
<tr>
<td>Caucasian</td>
<td>15 (83)</td>
</tr>
<tr>
<td>African American</td>
<td>3 (17)</td>
</tr>
<tr>
<td>ECOG performance status, n (%)</td>
<td>70</td>
</tr>
<tr>
<td>0</td>
<td>16 (89)</td>
</tr>
<tr>
<td>1</td>
<td>2 (11)</td>
</tr>
<tr>
<td>PSA (ng/mL), n = 18</td>
<td>119 (4-2,047)</td>
</tr>
<tr>
<td>PTH (pg/mL), n = 17</td>
<td>69 (32-396)</td>
</tr>
<tr>
<td>Patients with bone metastases, n (%)</td>
<td>14 (78)</td>
</tr>
<tr>
<td>Patients with elevated PTH, n (%)</td>
<td>7 (41)</td>
</tr>
<tr>
<td>Alkaline phosphatase (units/L), n = 17</td>
<td>118 (72-4,302)</td>
</tr>
<tr>
<td>Calcium (albumin corrected, mg/dL), n = 18</td>
<td>9.4 (8.1-10.2)</td>
</tr>
<tr>
<td>Albumin (g/dL), n = 18</td>
<td>4.1 (3.5-4.4)</td>
</tr>
<tr>
<td>Phosphorus (mg/dL), n = 18</td>
<td>3.5 (2.6-3.7)</td>
</tr>
<tr>
<td>Creatinine (mg/dL), n = 17</td>
<td>1.3 (1.1-1.7)</td>
</tr>
<tr>
<td>25-Hydroxyvitamin D (ng/mL), n = 16</td>
<td>19.5 (8-34)</td>
</tr>
<tr>
<td>Ca × P (mg²/dL², corrected), n = 18</td>
<td>31.6 (25.6-36.7)</td>
</tr>
</tbody>
</table>

NOTE: Data are given as medians and ranges.

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

*One patient, whose PSA at entry was <10, was entered into the trial in error.
experienced a grade 2 photosensitive rash that was consid-
ered to be drug related during cycle 1, week 6, of the 15-μg
dose. This resolved without intervention. Another patient had
grade 2 neutropenia that was possibly drug related.

Other observed effects were considered by the investiga-
tors not to be drug related. These include grade 4 thrombo-
cytopenia in a patient who had undergone right hemicolec-
tomy 3 days previously and subsequently died, grade 3 pneumonia
after 3 doses of the 25-μg dose in a patient who had a prior
history of pneumonia, grade 3 alkaline phosphatase in four
patients that was related to their advanced prostate cancer,
and grade 3 cardiac dysrhythmia (atrial fibrillation) in one
patient with a history of chronic atrial fibrillation on the 10-
μg dose after undergoing right hip replacement. This occurred
post-surgically 4 days after the last dose of paricalcitol. This
same patient had grade 3 leg edema that was considered to
be related to his advanced cancer and hip surgery. Eleven
patients reported mild dizziness and weakness. One patient
reported mild flu-like symptoms. Two patients experienced
urinary tract infections.

**Prostate-specific antigen response.** PSA continued to increase
in most men. However, one patient experienced a minimal
increase in PSA during 3 months of treatment (27-33 ng/mL),
and a second patient showed a decline in PSA from 2,136 to
1,648 (23% decline on the 10-μg dose). A third patient
experienced a large decline in PSA from 2,837 to 1,326 ng/mL
(53% decline on his second dose level of 15 μg) that was not
sustained at the 50% level. This patient had previously shown a
decline in PSA from 2,047 to 1,575 (23%) on the first dose
level of 10 μg.

**Calcium.** Hypocalcemia was defined as any value below the
laboratory reference value of 8.5 mg/dL, and hypercalcemia as
any value >10.5 mg/dL. Serum calcium was normalized to a
serum albumin concentration of 4.0 g/dL for any patient with
a serum albumin of <4.0 g/dL.

Four patients developed elevations in serum calcium during
treatment. Two of these had one measurement that was mildly
elevated (10.6 and 11.1 mg/dL) at the 5- and 20-μg doses,
respectively, which returned to normal levels. Another patient
showed a serum calcium of 11.5 and 11.7 mg/dL at the 15- and
20-μg doses. A fourth developed hypercalcemia at the 20-μg
dose, reaching a maximum of 14.3 mg/dL at the 25-μg dose,
when the patient came off study due to disease progression.

Conversely, 3 of 18 (17%) patients showed at least one
episode of hypocalcemia with values of 8.1, 8.4, and 8.3 mg/dL
at the 10-, 15-, and 20-μg doses.

**Phosphorus.** The lower and upper laboratory limits for
phosphorus were 2.7 and 4.5 mg/dL. Paricalcitol had little
effect on serum phosphorus levels, from a mean of 3.38 mg/
dl pretreatment to 3.39 mg/dL posttreatment. Only two
instances of mild hyperphosphatemia were observed during
the course of the study, in two patients, with serum levels of
4.6 and 5.0 mg/dL at the 15- and 25-μg doses, respectively.

Conversely, 5 of 18 (28%) patients developed at least one
instance of hypophosphatemia, with the lowest serum
phosphorus recorded being 1.9 mg/dL. One man who
developed hypophosphatemia was mildly hypophosphatemic
at study entry (2.6 mg/dL).

**25-Hydroxyvitamin D.** The laboratory reference range
for 25-hydroxyvitamin D was 10 to 68 ng/mL. Serum baseline
levels of 25-hydroxyvitamin D were normal in the majority
(14 of 16, 88%) of men. Two men showed borderline
hypovitaminosis D, with serum levels of 8 and 9 ng/mL.

**Calcium-phosphorus product.** The (albumin corrected) Ca × P
product was calculated for the 12 patients who remained on
study for at least 12 weeks. No clinically significant elevations
were observed. Paricalcitol had little effect on the Ca × P
product: the median (and range) values pretreatment and
posttreatment were 31.6 (25.6-36.7) and 30.0 (19.1-49.1),
respectively.

**Parathyroid hormone.** The lower and upper limits for intact
PTH were 8 and 72 pg/mL. Paricalcitol significantly reduced
serum PTH. The median PTH at entry into the study was
69 pg/mL (range, 3-396); the median posttreatment was
33.5 pg/mL (range, 5-237; \( P < 0.0004 \), paired t test).

Of the 17 men with baseline PTH values, seven (41%) had elevated
PTH levels. An additional two men presented with PTH levels
that were borderline (both 69 pg/mL). One patient, whose
duration on the trial was only 4 weeks, showed a decline in
PTH from 396 to 237 pg/mL (40%) after 2 weeks of therapy. Of
the seven men with abnormal levels, five returned to normal.

Four of the five normalizations occurred while the men were on
the first dose (5, 10, 15, and 20 μg); the fifth normalization
occurred on the second dose (15 μg). Two men who had
normal baseline PTH values developed elevated serum PTH
levels subsequently; one on the 5-μg dose, his first dose and one
on the 10-μg dose, his second dose.

The relationship between pretreatment and posttreatment
PTH is shown in Fig. 1.

**Alkaline phosphatase.** The upper laboratory limit for alkaline
phosphatases was 110 units/L. Pretreatment and posttreatment
values for alkaline phosphatase were available for 17 of 18
patients. At entry into the trial, alkaline phosphatase was
elevated in approximately half of the patients (median = 118),
reflecting the presence of bony metastases. Alkaline phospha-
tase levels continued to increase in 11 of 18 patients (median =
119; range, 27-2,419). They showed no change in one and
decayed in five patients.

**Survival.** As of August 10, 2005, all but one patient had
expired. The median survival was 9.0 months with a 95%
confidence interval of 8.5 to 22.2 months. The cause of death in
these men was prostate cancer (n = 15), myocardial infarction (n = 1), and post-surgical decline, following surgery for repair of a perforated bowel (n = 1).

The survival curve as a function of initial PTH is shown in Fig. 2. For every 25 pg/mL increase in PTH, the hazard increases 22% (95% confidence interval for hazard ratio, 1.03-1.43; \( P = 0.01 \), log-rank test). The estimated median survivals for baseline PTH of 3, 70, and 400 (which represent the minimum, median, and maximum baseline values in our trial) are 21.2, 10.7, and 4.0 months, respectively.

To determine whether the relationship between PTH and survival was independent of the extent of disease, we used serum PSA as a marker of extent of disease and did survival analyses using a Cox regression model that included both PSA and PTH variables in the model (18). In this model, the relationship between survival and initial PSA was not significant (\( P = 0.97 \), Wald test), but the effect of PTH remained significant (\( P = 0.02 \), Wald test). This indicates that the survival effect associated with PTH was present even after adjustment for disease severity.

**Discussion**

No patient in this trial showed a sustained 50% decrease in PSA, the primary end point. However, one patient, while on the 15-\( \mu \)g dose, experienced a large decline in PSA (2,837-1,326 ng/mL, 53%). This rose to 1,500 ng/mL on the next determination (a 47% decline), narrowly missing the criterion for a sustained decline. The same patient, while on the 10-\( \mu \)g dose, showed a drop in PSA from 2,047 to 1,575 (23%). Similar findings were reported by Osborn et al. (11) for 13 patients in the first clinical trial of oral calcitriol in AIPC, and for 22 patients treated with a high-dose formulation of oral calcitriol reported by Beer et al. (12). No patient in these studies showed a sustained 50% decline in PSA.

The maximally tolerated dose for paricalcitol was not reached in this study, although patients were treated with paricalcitol at doses 50% higher than those previously reported in the literature (i.e., 25 versus 16.8 \( \mu \)g; ref. 19). These doses were well tolerated. Eight (46%) patients reported mild nausea, consistent with reports of nausea in patients with end-stage renal disease treated with paricalcitol (20). The one patient who developed a grade 3 toxicity and a serum calcium of 14.3 mg/dL had a blocked nephrostomy tube the day before his blood draw. It is thus possible that his decreased excretion of urinary calcium contributed to his elevated serum calcium. Conversely, two men were hypocalcemic at study entry, with serum calcium of 8.1 and 8.2 mg/dL. Two other patients developed at least one episode of hypocalcemia during their treatment. The hypocalcemia was apparently not due to hypoalbuminemia, as no patient had serum albumin levels below the normal laboratory range (3.2 g/dL). Similarly, although two patients showed elevations in serum phosphorus, hypophosphatemia was more common, with six patients showing at least one instance of hypophosphatemia during the course of the study.

Few significant elevations in serum calcium in these men were observed. Similarly, no significant elevations in \( \text{Ca} \times \text{P} \) product were seen. The current recommendation for the \( \text{Ca} \times \text{P} \) product in chronic kidney disease and in the dialysis population is \( \leq 55 \text{mg}^2/\text{dL}^2 \) (21). Our results were well below this limit: the median posttreatment \( \text{Ca} \times \text{P} \) product was 30.0, and the highest observed value was 49. It is likely that the tendency of metastatic prostate cancer to be associated with hypocalcemia rather than hypercalcemia increases the therapeutic window for calcitriol analogues in this population.

Clinical trials in the dialysis population have shown that paricalcitol reduces serum levels of alkaline phosphatase, indicating a reduction in bone remodeling (22). Pretreatment and 12 week posttreatment levels of alkaline phosphatase were available for 17 of our patients. One showed no change in alkaline phosphatase levels, 11 of 17 (65%) showed increases, and 5 of 17 (29%) showed declines. This suggests that paricalcitol may reduce bone remodeling in some patients even in the presence of rising PSA.

In patients with chronic renal failure, the peak serum concentration of paricalcitol was 4.4 ± 1.6 × 10^{-9} \text{mol/L} after a dose of 0.24 \( \mu \)g/kg (16.8 \( \mu \)g). This is the recommended maximum dose in the treatment of secondary hyperparathyroidism (18). In our trial, considerably higher doses did not result in frequent hypercalcemia or in an elevated \( \text{Ca} \times \text{P} \) product. Our previous laboratory studies showed a 20% inhibition in the proliferation of primary cultures of prostate cancer cells exposed to paricalcitol at 10^{-9} \text{mol/L}, suggesting that some inhibition of prostate cell growth in vivo might be achievable at these doses (17). Because the maximally tolerated dose was not reached in this study, further study of paricalcitol at higher doses would be valuable.

Upon entry into the study, elevations in serum PTH were found in 7 of 17 (41%) men; an additional two (12%) had PTH levels that were borderline. Treatment with paricalcitol significantly reduced PTH in these men. Low serum calcium and high serum PTH are common but often unrecognized features of advanced prostate cancer. For example, in a series of 75 prostate cancer patients with bony metastases, hypocalcemia occurred during the course of the disease in 31% (23). Murray et al. reported a series of 146 unselected patients with advanced prostate cancer (24). The prevalence of elevated PTH in that series was 34% and was >50% in patients with bony metastases. These findings are in keeping with the "hungry tumor
phenomenon” (25) or “bone hunger syndrome” (26), in which osteoblastic metastases cause increased deposition of calcium into bone. The resulting hypocalcemia causes an elevation in serum PTH (i.e., secondary hyperparathyroidism; ref. 27). Chronic kidney disease and/or vitamin D deficiency are common causes of secondary hyperparathyroidism. However, in the majority of our patients, serum levels of creatinine and of 25-hydroxyvitamin D were within the normal laboratory ranges (88% and 83%, respectively). This suggests that the “hungry bone” and not kidney disease or vitamin D deficiency was the predominant cause of the elevated PTH.

Although elevated serum PTH that is associated with vitamin D deficiency may be treated with supplemental vitamin D and/or calcium (21), elevated PTH caused by hungry bone may be refractory to these first-line therapies (e.g., ref. 28). Vitamin D deficiency traditionally was defined as 25-hydroxyvitamin D ≤ 10 ng/mL (25 nmol/L), as this value is associated with rickets in children and osteomalacia in adults (29). Recently, the term vitamin D insufficiency (synonyms, mild, moderate vitamin D deficiency; 10-20 and 5-10 ng/mL, respectively) has been used to describe less severe deficiency that is associated with elevated serum PTH. A value of 20 ng/mL (50 nmol/L) is commonly used to define vitamin D insufficiency as this is the threshold above which serum PTH levels are not decreased by vitamin D supplements (30).

The median 25-hydroxyvitamin D in our study was 19.5 ng/mL. Thus, vitamin D supplements would be expected to lower PTH in only half of these patients. Moreover, the magnitude of the PTH elevation caused by mild vitamin D deficiency is <15% (30). Thus, vitamin D supplements would be expected to have a modest effect in PTH reduction and only in those patients with mild vitamin D deficiency.

To our knowledge, the only published attempt to reduce PTH in patients with advanced prostate cancer with calcium supplements was that of Murray et al. (24). These authors treated 32 patients with elevated PTH with oral calcium (600 mg Caltrate twice daily, increasing to 1,200 mg). PTH levels fell initially but returned to pretreatment levels by 3 months, despite continuing supplementation. These authors hypothesized that large amounts of calcium may be needed to significantly raise serum calcium and thereby depress serum PTH in this population. Our data indicate that the elevated serum PTH in men with advanced prostate cancer was effectively depressed by paricalcitol. An important potential advantage of paricalcitol in this setting is that paricalcitol is known to inhibit the proliferation of prostate cancer cells.

Elevated serum levels of PTH are associated with increased mortality from cardiovascular disease in the dialysis population (31). Moreover, recent literature suggests that elevated serum levels of PTH may have additional deleterious effects in advanced prostate cancer. For example, in *vivo*, PTH increases the proliferation of androgen-insensitive DU-145 human prostate cancer cells and increases chemotaxis in three human prostate cancer cell lines (32). In *vivo*, the incidence of skeletal metastatic foci was significantly increased in mice treated with PTH versus mice treated with saline control (33). In men with prostate cancer (without evidence of bone metastases), the infusion of PTH increased serum and urinary levels of N-telopeptide (34), a marker of bone resorption that has been correlated prospectively with the progression of bony metastases (35) and with the frequency of skeletal complications (36). Finally, our data indicate that initial serum levels of PTH were negatively and significantly associated with survival, and this effect was independent of disease severity as measured by PSA. Together, these studies support the hypothesis that PTH increases the proliferation and metastasis of prostate cancer cells and suggests the desirability of PTH suppression in prostate cancer patients with elevated PTH.

Previous trials of calcitriol and analogues in prostate cancer have focused either on PSA response and/or survival. To our knowledge, this is the first trial that specifically addressed PTH. We observed that paricalcitol, which was designed to suppress PTH in patients with chronic renal disease, significantly suppressed PTH in men with advanced prostate cancer. Whether PTH suppression in this population is associated with increased survival and/or improved quality of life are important issues that could be addressed by future clinical trials.

In prostate cancer cells in *vivo*, we showed previously that paricalcitol acts synergistically with ionizing radiation to increase the efficacy of ionizing radiation to induce prostate cancer cell kill at therapeutically relevant doses (1-2 Gy; ref. 37). Importantly, paricalcitol did not induce significant radiosensitization of normal prostate epithelial cells. This suggests that paricalcitol also may have use as an adjuvant to ionizing radiation. The capsule formulation of paricalcitol, which has recently been approved for the prevention and treatment of secondary hyperparathyroidism in stage 3 and 4 chronic kidney disease patients, should facilitate clinical investigations of paricalcitol in prostate cancer.

References

Clinical Cancer Research

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