A Phase I Trial of Calcitriol (1,25-Dihydroxycholecalciferol) in Patients with Advanced Malignancy

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ABSTRACT
Vitamin D is a steroid hormone best known for its activity in regulating calcium and bone metabolism. Epidemiological evidence suggests that vitamin D may play a role in inhibiting the development of colon and prostate cancer. Vitamin D receptors are expressed in many types of malignant cells; in vitro and in vivo vitamin D and vitamin D analogues are active in suppressing the development and inhibiting the growth of numerous human and animal tumors. The major toxicity of the active form of vitamin D, 1,25-dihydroxycholecalciferol (calcitriol), is the induction of hypercalcemia. There are no data indicating the maximum tolerated dose of calcitriol administered every other day (QOD) s.c. We hypothesized that this route and schedule would permit administration of higher doses of calcitriol, which might have anticancer activity. We conducted a Phase I trial of calcitriol given s.c. QOD in patients with advanced solid tumors. Thirty-six patients were entered at doses ranging from 2 to 10 μg QOD; dose-limiting toxicity (hypercalcemia) occurred in three of three patients entered at the 10-μg QOD dose. Hypercalcuria occurred at all dose levels examined. No other toxicity was seen. Assessment of serum calcitriol concentrations by a RIA revealed a decrease in the induction of hypercalcemia. There are no data indicating the maximum tolerated dose of calcitriol administered every other day (QOD) s.c. We hypothesized that this route and schedule would permit administration of higher doses of calcitriol, which might have anticancer activity. We conducted a Phase I trial of calcitriol given s.c. QOD in patients with advanced solid tumors. Thirty-six patients were entered at doses ranging from 2 to 10 μg QOD; dose-limiting toxicity (hypercalcemia) occurred in three of three patients entered at the 10-μg QOD dose. Hypercalcuria occurred at all dose levels examined. No other toxicity was seen. Assessment of serum calcitriol concentrations by a RIA revealed a decrease in the maximum serum levels occurred at the 10-μg QOD dose: 288 ± 74 and 321 ± 36 pg/ml at days 1 and 7, respectively. The normal range of calcitriol serum concentration, determined using this assay, is 16–56 pg/ml. Serum calcitriol levels were maintained at near peak concentrations for at least 8 h following s.c. injection. This study indicates that substantial doses of calcitriol can be administered via this route with tolerable toxicity. Studies to explore approaches to ameliorate the hypercalcemia induced by calcitriol and to explore alternative schedules and interactions with other agents are warranted.

INTRODUCTION
Vitamin D is a steroid hormone best known for its activity in regulating calcium and bone metabolism. Precursors of vitamin D are metabolized in the skin and, subsequently, the liver and kidney to the most active form, calcitriol (1,25-dihydroxycholecalciferol). Epidemiological evidence suggests that vitamin D may play an important role in the development of colon and prostate cancer; low vitamin D serum levels, low vitamin D intake, and decreased UV light activation of vitamin D in the skin are associated with an increased risk of these tumors (1–4). There is also evidence that dietary supplementation with vitamin D can reduce the incidence of colon cancer (5). VDR polymorphisms, which may influence the activity of vitamin D, have been associated with differing risks of prostate and breast cancer (6, 7).

In vitro and in vivo, calcitriol has antiproliferative and differentiating effects on human and animal tumors (8–17). Previous studies in our laboratory have demonstrated growth inhibition in murine SCC cells (18) and in two rat prostate adenocarcinoma cell lines (Dunning AT-2 and MLL) in vitro (19). In vivo calcitriol inhibits the growth of established tumors and tumor outgrowth in murine SCC and both primary and metastatic growth in the Dunning MLL tumor (18, 19). Calcitriol also effects the development of normal tissues (e.g., prostate). Konety et al. (20) demonstrated that calcitriol alters the growth and differentiation of the normal prostate in an in vivo model.

The mechanism by which calcitriol exerts its antiproliferative and differentiating effects is not clear; specific VDRs are required for these effects to occur. High-affinity VDRs have been described in normal colon and prostatic epithelial cells, primary tumors from several sites, and multiple cell lines (8, 11, 21–31). The wide distribution of these receptors suggests that calcitriol may play a role in the function of a number of normal and malignant tissues. In the mouse SCC and Dunning MLL models, growth is inhibited only in tumors with VDRs (13, 18, 19, 21). Similar tumors without VDRs are resistant to the growth-inhibitory effect of calcitriol. Inhibition of anchorage-

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4 The abbreviations used are: VDR, vitamin D receptor; SCC, squamous cell carcinoma; MTD, maximum tolerated dose; QOD, every other day; PTH, parathyroid hormone; HPLC, high-performance liquid chromatography; AUC, area under the concentration-time curve; CEA, carcinoembryonic antigen.
independent growth of cell lines by calcitriol is associated with the number of VDRs per cell (32).

Oral calcitriol has been used as an antineoplastic agent in a number of clinical trials. Little evidence of efficacy has been seen, and calcitriol administration has been limited by the development of hypercalcemia (33–36). Calcitriol causes hypercalcemia by increasing intestinal calcium absorption and mobilizing bone stores (37). Because there may be a direct effect of calcitriol on the intestinal mucosa, one approach to limiting hypercalcemia would be to administer calcitriol parenterally, i.v.

Calcitriol causes hypercalcemia by increasing intestinal calcium absorption and mobilizing bone stores (37). Because there may be a direct effect of calcitriol on the intestinal mucosa, one approach to limiting hypercalcemia would be to administer calcitriol parenterally, i.v. and s.c. administration of calcitriol at doses of 1.5–4 μg three times per week have been used in individuals with renal disease (38–40).

To determine the MTD of calcitriol that could be administered via s.c. injection, we conducted this Phase I trial in patients with advanced malignancies. As a secondary objective, we sought to describe the pharmacokinetics of parenterally administered calcitriol, both with the initial dose and following the first week of therapy.

**Materials and Methods**

Patients eligible for this trial had a histologically confirmed diagnosis of advanced cancer that was not curable by standard therapies; a Eastern Cooperative Oncology Group performance status of 0–2; and adequate bone marrow (absolute neutrophil count, >1,500/ml; platelet count, >100,000/ml), renal (creatinine, <2.0 mg/dl), and hepatic (bilirubin, <2.0 mg/dl; aspartate aminotransferase, <4 times the institutional upper limit of normal) function. Corrected serum calcium was also required to be <10.5 mg/dl at study entry. Patients with brain metastases were eligible for this trial following definitive radiotherapy. Patients receiving glucocorticoids at doses higher than physiological replacement were ineligible. Patients with any history of significant cardiac dysrhythmia, unstable angina, coronary artery disease, diabetes mellitus, glaucoma, or reaction to prior steroid therapy were excluded. After observing nephrolithiasis in three patients early in the trial, any patient with a prior history of nephrolithiasis or any patient who had undergone a prior nephrectomy was excluded from participation. All patients provided written informed consent, and the protocol and consent form were approved by the Biomedical Institutional Review Board at the University of Pittsburgh.

**Study Plan.** At study entry, all patients underwent a complete physical exam and laboratory evaluation, including complete blood count and serum chemistries. At the initiation of therapy, patients were admitted to the General Clinical Research Center of the University of Pittsburgh. They received their initial injection of s.c. calcitriol at ~11:00 am on the first study day. Plasma samples were obtained for calcitriol pharmacokinetics on days 1 and 7 (see below). While they were on the study, patients were monitored with weekly complete blood counts and measurements of electrolyte, blood urea nitrogen, and creatinine levels and twice-weekly measurements of serum calcium levels. A 24-h urine calcium was collected monthly in patients entered at the four highest doses of calcitriol. Physical examination and toxicity assessment were performed every 4 weeks.

**Dose Escalation and Modification.** Three patients were enrolled initially at each dose level. All three patients at a given dose level were observed for at least 2 weeks before patients were enrolled at the next dose level. Dose-limiting toxicity was defined as symptomatic hypercalcemia at any serum calcium level of ≥10.5 mg/dl. Calcium level of ≥12.0 mg/dl, even if the patient was asymptomatic. Other dose-limiting toxicities included any unexpected grade 3 toxicity, with the exception of lymphocytopenia, alopecia, nausea, or vomiting. If none of the patients treated at a given dose level had dose-limiting toxicity, the next patient was enrolled at the subsequent dose level. If one or two of the three patients initially enrolled at a dose level developed a dose-limiting toxicity, three additional patients were enrolled at that level. The MTD was defined as the dose level immediately below that at which three of three or three or more of six patients developed dose-limiting toxicity. The starting dose was 2 μg s.c. QOD. Initially, dose was escalated in 1-μg increments. After the 8-μg dose was reached, subsequent escalations were in 25–30% increments. Thus, the dose level following the 8 μg dose was 10 μg. Subsequent planned escalations were to 13 and 17 μg, respectively. Because the expected toxicity of calcitriol was well defined and easily measured, patients who had no toxicity on a given dose level were eligible for escalation of the dose to the next dose level once all three patients enrolled at that dose level had completed two weeks of therapy without dose-limiting toxicity. Patients were maintained on therapy until they had evidence of progressive disease or intolerable toxicity.

**Calcitriol Pharmacokinetics and PTH Determinations.** Pharmacokinetic blood sampling was performed on days 1 and 7 of calcitriol therapy. The calcitriol dose ranged from 2–10 μg administered by s.c. injection. Plasma samples were separated by centrifugation from 8 ml of heparinized blood collected prior to calcitriol administration and at 0.5, 0.75, 1.5, 2, 2.5, 3, 4, 6, 8, and 12 h post-drug administration. All plasma samples were stored at −20°C until assay. Plasma samples from all patients were analyzed by RIA using a 1,25-dihydroxyvitamin D $^{125}$I-RIA Kit from Incstar Corp. (Stillwater, MN). Serum PTH was determined using a standard commercial RIA (Incstar Corp.)

**Performance Characteristics of Calcitriol RIA.** 1,25-Dihydroxyvitamin D$_3$ $^{125}$I-RIA assay has intra- and interassay coefficients of variation of 12 and 20%, respectively. The lower limit of detection is ~2 pg/ml. Although we have not evaluated the degree of cross-reactivity with other vitamin D metabolites in our clinical samples, this RIA is known to cross-react with 1,25-(OH)$_2$D$_2$. Pretreatment of protein-free serum extracts with sodium peroxidate destroys 1,25-(OH)$_3$D$_2$, 23,26-lactone, a metabolite of calcitriol known to interfere with the RIA. The same plasma calcitriol concentrations were noted when samples were assayed by RIA before and after normal-phase HPLC separation and collection of calcitriol peak. HPLC separation of calcitriol from other metabolites of vitamin D was achieved on a Zorbax column (250 × 4.6 mm) using hexane/isopropanol/methanol (84:10:6) at a flow rate of 2 ml/min as the mobile. Under this condition, calcitriol retention time is 5.4 min and is monitored at 265 nm.

**Data Analysis.** $T_{max}$, the time to peak plasma concentration ($C_{max}$), and plasma steady-state levels ($C_{ss}$) were deter-
mined by visual inspection followed by calculation of the mean value in the case of $C_{ss\text{max}}$. The AUC over the first 12 h following a single s.c. dose of calcitriol on days 1 and 7 of therapy was estimated by the trapezoidal rule. The PHARM/PCS computer program (41) was used for all calculations.

RESULTS

A total of 36 patients (24 men and 12 women) were enrolled in this trial; 4 were African-American and 32 were Caucasian, and the median age was 63 years (range, 16–78 years). The majority of patients had adenocarcinoma, with most originating in the gastrointestinal tract. All 36 patients had previously undergone surgery, 30 had received prior chemotherapy, and 19 had received prior radiation therapy. Patients were treated at eight different dose levels of calcitriol. The numbers of patients enrolled at each dose level and with dose-limiting toxicity are summarized in Table 1. Three of three patients enrolled at the 10-μg QOD dose developed dose-limiting toxicity. The MTD for s.c. calcitriol given QOD was 8 μg, a dose at which none of the six patients developed hypercalcemia.

As anticipated, the dose-limiting toxicity was hypercalcemia. This was seen in all three patients enrolled at the 10-μg dose. Four patients developed hypercalcemia at lower doses of calcitriol. The first of these occurred at the 2.0-μg dose level. Upon close questioning, it was determined that this patient was probably not administering his dose of calcitriol appropriately and was likely administering excessive doses. With instruction, the patient had no further incidence of hypercalcemia, but developed progressive disease and went off the study. An additional three patients were enrolled at this dose level; none developed hypercalcemia. A patient with prostate cancer at the 4-μg dose level also developed hypercalcemia after 80 days of treatment. Because of the late onset of hypercalcemia in this patient, additional patients had already been entered at the next dose level. Two patients at the 5.0-μg dose developed hypercalcemia; one patient with SCC of the head and neck developed hypercalcemia within the first week of treatment. The second patient had mesothelioma. Additional patients were entered at this dose level; no major toxicities or hypercalcemia occurred, and dose escalation continued. Plasma calcitriol levels (days 1 and 7) were not clearly different for these patients than for those

Table 1

| Calcitriol dose (μg) | No. of patients | No. of patients with DLTa | Average maximum serum calcium (mg/dl) | Fold change in 24-h urine calcium, pretherapy vs. day 28 | SD
<table>
<thead>
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<td>+1.9</td>
<td>ND</td>
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*DLT, dose-limiting toxicity; ND, not determined.

Table 2

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<th>Dose (μg)</th>
<th>n</th>
<th>$T_{\text{max}}$ (h)</th>
<th>$C_{\text{ss\text{max}}}$ (pg/ml)</th>
<th>AUC0–12 h (pg·h/ml)</th>
<th>$T_{1/2}$ (min)</th>
<th>$T_{1/3}$ (min)</th>
<th>$V_{dss}$ (liters)</th>
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<td>2</td>
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<td>0.9 ± 0.3</td>
<td>23 ± 6</td>
<td>112 ± 16</td>
<td>10.6 ± 2.1</td>
<td>121 ± 16</td>
<td>246 ± 12</td>
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<tr>
<td>3</td>
<td>3</td>
<td>1.5 ± 0.1</td>
<td>31 ± 2</td>
<td>144 ± 12</td>
<td>12.4 ± 2.5</td>
<td>168 ± 12</td>
<td>351 ± 25</td>
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<td>4</td>
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<td>2.7 ± 0.9</td>
<td>41 ± 1</td>
<td>171 ± 12</td>
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<td>195 ± 12</td>
<td>426 ± 25</td>
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<td>5</td>
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<td>3.2 ± 0.5</td>
<td>51 ± 1</td>
<td>186 ± 12</td>
<td>15.6 ± 2.5</td>
<td>211 ± 12</td>
<td>495 ± 25</td>
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<td>4.0 ± 0.4</td>
<td>58 ± 2</td>
<td>201 ± 12</td>
<td>18.2 ± 2.5</td>
<td>227 ± 12</td>
<td>570 ± 25</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>4.8 ± 0.5</td>
<td>66 ± 2</td>
<td>216 ± 12</td>
<td>20.8 ± 2.5</td>
<td>243 ± 12</td>
<td>650 ± 25</td>
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<tr>
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<td>5.7 ± 0.6</td>
<td>74 ± 2</td>
<td>231 ± 12</td>
<td>23.4 ± 2.5</td>
<td>260 ± 12</td>
<td>730 ± 25</td>
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<td>10</td>
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<td>7.0 ± 0.7</td>
<td>82 ± 2</td>
<td>246 ± 12</td>
<td>26.0 ± 2.5</td>
<td>276 ± 12</td>
<td>810 ± 25</td>
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*Values are mean ± SE.
who received similar doses. Calcitriol-induced hypercalcemia was commonly observed in the second and third weeks of therapy. Calcitriol-induced hypercalcemia resolved within 1 week of terminating therapy.

No other consistent toxicities meeting the definition of dose-limiting toxicity were seen on this trial. Three patients with diffuse bony metastases secondary to prostate cancer did experience increased bone pain after initiation of calcitriol therapy. The interpretation of this observation in patients with progressive bony metastasis is unclear. Three patients were recognized to have nephrolithiasis after cessation of calcitriol: in two, nephrolithiasis was symptomatic, and in the third, an incidental renal stone was discovered upon abdominal imaging.

Although response was not the primary end point of this trial, patients did undergo response assessment at regular intervals, and no responses were seen. Several patients at the lower dose levels had stable disease and were able to tolerate therapy up to 4 months in duration. The majority of patients, however, developed progressive disease, and this was the reason for discontinuation of therapy.

Six patients with prostate cancer were entered, all at doses of 6 μg QOD or less. Prostatic-specific antigen was monitored monthly and increased by >50% in each patient by 2 or 3 months of therapy. In each patient whose prostate-specific antigen increased other manifestations of progressive disease (pain and new lesions on bone scan) also developed. CEA was assessed serially in two patients with colorectal cancer. In one patient, CEA increased (from 796 to 1205 mg/dl), and physical evidence of progressive disease was evident at day 58. The second patient developed radiographic evidence of progressive disease on day 149, and CEA had increased from 533 to 663 mg/dl.

Although the number of patients in which pharmacodynamic estimations can be made is limited, there does appear to be a clear and expected relationship between the dose of calcitriol administered and the maximum average change in serum calcium seen over the first 28 days of therapy; urine calcium increased substantially in all patients in whom it was determined (Table 1). Observed and calculated pharmacokinetic parameters for calcitriol after s.c. administration are shown in Table 2. Most of the patients analyzed had day 1 pretreatment plasma calcitriol levels within the reported physiological level (19–74 pg/ml; Ref. 42). One patient with low pretreatment calcitriol plasma content (6 pg/ml) had adenocarcinoma of the colon, and a patient with high calcitriol serum content (130.3 pg/ml) had carcinoma of the gallbladder. Neither of these patients had biochemical or clinical evidence of renal function impairment. As the dose of calcitriol increased, the mean AUC at each dose level of individual patients increased (Fig. 1).

Profiles of the plasma concentrations following s.c. administration of 2, 4, 6, 8, and 10 μg of calcitriol are shown in Fig. 2. Examination of these profiles suggest the existence of three pharmacokinetic phases: the initial rapid absorption (C_{pmax} at 2 h) of calcitriol from s.c. tissues, a second phase in which plasma calcitriol remains constant for ~6 h, and a third phase starting 8 h after administration in which calcitriol plasma levels decline. The duration of the third phase has not been determined because our sampling terminated at the 12-h time point. It should be noted that, on day 7 (48 h after the last dose of calcitriol), pretreatment calcitriol plasma levels were within the normal physiological range in all patients tested (n = 29). Between 2 and 8 h after s.c. administration, plasma concentrations of calcitriol remained relatively unchanged at all dose levels. Although the volume of injection increased at higher calcitriol doses, it was administered in small volumes at multiple sites. This observation may, therefore, be attributed to a non-dose-
Fig. 3 Serum PTH levels on days 1 and 7 at each dose of calcitriol. Decreases (---) or increases (••••) in PTH from day 1 (○) to day 7 (■) are shown. Each line represents results from an individual patient.

DISCUSSION

This study demonstrates that s.c. calcitriol can be administered safely at doses up to 4–5-fold higher than the usual oral replacement dose of 1.5–2.0 μg per day. Therapy was well tolerated, and toxicities associated with this treatment were minimal. As anticipated, hypercalcemia was the dose-limiting toxicity, occurring in all patients treated above the 8.0-μg QOD dose. Four patients treated at lower doses also developed symptomatic hypercalcemia. In one patient, this was attributable to compliance problems. In the other three, the etiology of this inconsistent response to exogenous calcitriol is unclear. We do not have evidence of unusually high blood levels on days 1 or 7 in these three patients. Hypercalcemia at the lower dose levels may be related to variations in pretreatment vitamin D total body content, differences in gastrointestinal or bone responsiveness determined by mechanisms other than total vitamin D tissue levels, or alterations in vitamin D-binding protein levels which would result in variations in free or active calcitriol. Renal stones developed in three patients on this trial. The hypercalcemia that accompanies calcitriol administration would be expected to enhance the potential for stone formation. After entry criteria excluded patients with a past history of stone formation, no further cases of nephrolithiasis were detected. Further studies of calcitriol or vitamin D analogues will require vigilance with respect to the formation of renal stones.

The calcitriol AUC_{0-12 h} value of 846 ± 59 pg h/ml after s.c. administration of the 2-μg dose is similar to the 790 pg h/ml following oral ingestion of an equivalent dose (37). C_{pmax}, T_{pmax}, and AUC values after the 2-μg dose in this trial are similar to data reported by Selgas et al. (39) who studied s.c. calcitriol in dialysis patients. This is the first report, of which we are aware, to evaluate the pharmacokinetics of calcitriol administered s.c. at doses of >4 μg. Results of pharmacokinetic studies of 2- and 4-μg doses of s.c. administered calcitriol in end-stage renal disease (39) and our cancer patients are, however, very similar.

Although analysis of pharmacokinetic data obtained at the higher doses of calcitriol generally are consistent with the data obtained at lower doses, evidence of inducible mechanisms of clearance was seen at higher doses. Day 7 AUC and t_{1/2} were reduced without change in absorption rate constant. Previous studies at much lower doses have failed to demonstrate evidence of variations in pharmacokinetics or metabolism with continuous therapy (43). Although inspection of data suggest the possibility of a plateau in C_{ss} despite the increasing dose administered, we have not been able to confirm this possibility on careful analysis. Such studies will be examined in our ongoing trials. Following s.c. administration, C_{pmax} was observed within 2 h, unlike the i.v. and oral routes, in which C_{pmax} levels are seen within minutes and at ~4–6 h, respectively (38, 44). C_{pmax} after oral and i.v. routes are immediately followed by a steady decline in plasma calcitriol levels; however, a 6-h period of sustained steady-state plasma concentrations was seen following s.c. administration of high doses. The genesis of this difference is unclear. Among the possible explanations are different modes of metabolism and clearance following s.c. administration, which may diminish hepatic and pulmonary first pass effects compared to oral and i.v. administration, respectively. Higher doses of calcitriol administered in this trial may result in formation of metabolites with longer half-lives that cross-react with the RIA for calcitriol used. Also, the rate of absorption (depot/slow release concept) from the s.c. site may be an explanation for the sustained concentration of calcitriol in plasma. We will study this important issue further in the continuation of our studies of high-dose calcitriol and have developed a HPLC...
methodology to more carefully evaluate calcitriol pharmacokinetics and metabolism.

Calcitriol clearly exerts anticancer effects in many in vitro and in vivo systems. Unfortunately, no significant antitumor responses were demonstrated in this trial. This may reflect the problems inherent in the Phase I trial design in which patients with a variety of tumors are treated and a series of escalating doses are used. Although plasma levels demonstrate a marked increase in serum calcitriol as compared to endogenous levels, whether these levels are sufficient to result in the type of antitumor activity seen with high-dose calcitriol in rat and mouse in vivo models is unclear. Animal studies clearly indicate that the antitumor effects of calcitriol are dose related, and hence, continued exploration of ways in which higher doses of calcitriol may be administered is warranted. Among the maneuvers we continue to examine are dietary calcium restriction and concomitant administration of glucocorticoids. We have shown in murine models that glucocorticoid administration clearly reduces the severity of hypercalcemia and potentiates the antitumor effects of calcitriol in several model systems (21). A major determinant of serum calcium at any given serum concentration of calcitriol is the dietary intake of calcium (45, 46). Therefore, we are optimistic that further dose escalation of calcitriol will be possible with these maneuvers. In addition, analogues of calcitriol which are less potent in inducing hypercalcemia are available and are entering clinical trials (47). The MTD for this trial is >5 times the 1.5-μg daily dose, which was recently demonstrated to induce hypercalcemia in 3 of 13 men with prostate cancer (36). This suggests that further exploration of maneuvers to allow administration of higher doses of calcitriol may have merit.

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REFERENCES


