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Vitamin D and cancer: Clinical aspects

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Abstract

There are substantial preclinical and epidemiologic data that suggest that vitamin D plays a role in the prevention and treatment of cancer. Numerous observational studies have shown that low blood levels of 25(OH) vitamin D (cholecalciferol), estimated by geographical location, diet and activity assessment or measured serum levels are associated with a higher risk of cancer and worse cancer-specific survival as well as numerous morbidities to e.g. cardiovascular disease, stroke, infection, autoimmune disease, and neuromuscular dysfunction among large populations. A considerable number of *in vitro* and *in vivo* studies indicate that the most active metabolite of vitamin D – 1,25-dihydroxycholecalciferol or calcitriol – has anti-proliferative, pro-apoptotic, pro-differentiating, and anti-angiogenic properties. Combined treatment of calcitriol and many types of cytotoxic agents has synergistic or at least additive effects. However, clinical trials testing these hypotheses have been less encouraging, though a number of methodological, pharmacological, and pharmaceutical issues confound all trials ever conducted. In order to properly assess the clinical value of vitamin D, its metabolites and analogs in cancer prevention and treatment, more studies are needed.

Keywords

calcitriol; vitamin D; clinical trials

Introduction

In recent years a large number of observational and experimental studies have been undertaken to investigate the role of vitamin D and its metabolites in cancer.^{1–4} Vitamin D is a hormone produced through a multistep process initiated in the skin with conversion of 7-dehydrocholesterol to cholecalciferol (D3) upon exposure to ultraviolet B radiation. When

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cholecalciferol, or the plant derived derivative ergocalciferol, enters the circulation through epidermal transfer or after ingestion and intestinal absorption, it associates with vitamin D-binding protein. In this form it travels to the liver where it is hydroxylated to form 25(OH) vitamin D, the most abundant circulating form of vitamin D. The conversion of 25(OH) vitamin D to 1,25-dihydroxyvitamin D ($1,25(\text{OH})_2\text{D}$ or calcitriol) occurs predominantly in the kidneys, but other normal and neoplastic tissues are known to express 1- α -hydroxylase, suggesting that this enzymatic reaction also takes place in other sites in the body. Calcitriol together with parathyroid hormone (PTH) maintains proper levels of calcium in the blood, and if calcium is not available from dietary sources, normal levels are maintained at the expense of bone loss.⁵ In addition to these bone and mineral effects,⁶ vitamin D compounds have anticancer properties.^{7–17} For the purposes of this article we will focus primarily on the clinical applications of vitamin D and its metabolites in cancer treatment.

Although many foods in the US are fortified with vitamin D, the main source of the nutrient comes from its synthesis in the skin upon exposure to the ultraviolet B radiation from the sun.^{18–20} A National Health and Nutrition Evaluation Survey (NHANES) has estimated that an average individual's food intake of vitamin D in the United States is 200 IU/day; the recently updated recommended dietary allowance by the Institute of Medicine is 600 IU/day for most healthy adults and 800 IU/day for those over the age of 70.^{21–24} The definition of the "correct" levels and the role or necessity for supplementation of vitamin D to improve health and prevent disease are controversial. While some researchers claim that vitamin D deficiency is overestimated, others believe that most of the US population does not get enough of the nutrient from sun exposure and diet. Dialog in health and research communities has become so heated that it prompted the Agency for Healthcare Research and Quality (AHRQ) to charge the Institute of Medicine with the task of revisiting previous recommendations. As a consequence, an IOM study resulted in a new set of recommendations that were issued in the consensus study, "Dietary Reference Intakes for Calcium and Vitamin D," in late 2010.²¹ Although the IOM committee concluded that most North Americans are getting enough vitamin D, the new study recommended a daily increase of vitamin D for some groups compared to the recommendations established in a previous IOM report from 1997.²¹ The report also noted that in contrast to the large body of literature conclusively indicating an important role of vitamin D in skeletal health, the use of vitamin D in cancer chemoprevention and treatment remains ambiguous and inconclusive.²¹ The ambiguity arises from two aspects of the potential clinical utility of vitamin D that have to be evaluated independently of one another. First, preclinical data show that calcitriol elicits its anti-tumor properties at high systemic concentrations. Second, there is no agreed-upon definition of what levels of 25(OH) vitamin D in healthy individuals are adequate to protect against cancer.²⁵

The most widely used indicator of vitamin D status in the body is 25 hydroxyvitamin D₃, a precursor of calcitriol.⁵ The longer half-life of 25(OH) vitamin D (~ 3 weeks) makes this metabolite the most suitable surrogate marker of body vitamin D stores when compared to other vitamin D metabolites.⁵ 25(OH) vitamin D levels are usually determined by measurement of the metabolite in the plasma or serum. It is important to note, however, that the levels of 25(OH) vitamin D which are ideal or appropriate are not known. The levels constituting deficiency or insufficiency are somewhat arbitrarily based on associations of

25(OH)D3 levels and bone mineral density (BMD) or PTH hormone levels. Using these measures it is generally agreed that levels of 25(OH)D3 below or equal to 20 ng/ml and below or equal to 30 ng/ml represent vitamin D deficiency and insufficiency, respectively. The recommended form for replacement therapy is vitamin D3 (cholecalciferol), since it seems to be more potent than D2 (ergocalciferol)⁵ and D3 is detectable by all commercial assays.

The 2010 IOM consensus analysis noted that the majority of data regarding the impact of vitamin D on extraskeletal health outcomes, including cancer are inconsistent in several respects.²¹ First, only individuals with levels of 25(OH) vitamin D below 12 ng/ml are considered vitamin D deficient, and 20 ng/ml found to be the level that is needed for good bone health for practically all healthy individuals(21). Second, multiple factors such as diet, sun exposure, adipose tissue content, and skin pigmentation play critical roles in an individual's 25(OH) vitamin D systemic levels.²⁶ Last, the IOM report that recommended 4000 IU daily be the upper safe level of supplementation for large unmonitored populations.²¹

Epidemiologic link

There is considerable controversy regarding the role of vitamin D in cancer risk, incidence, and mortality as there are numerous conflicting data. The first study suggesting an association between vitamin D and cancer incidence or outcome was the seminal study of Garland and Garland.²⁷ They noted increased colon cancer mortality in populations residing in the northeastern United States where there is less exposure to solar radiation throughout the year, and higher mortality among people living in the southern, southwestern, and western portions of the US. These findings led the Garland brothers to suggest that greater UV light exposure led to increased systemic levels of vitamin D and that vitamin D may decrease the risk of colon cancer death. Numerous observational studies followed up on this concept and found associations between geographic distribution and vitamin D serum levels, and geographic site of residence and cancer incidence and mortality.^{28–32} A clear and unequivocal causal link between geographic location, UV irradiation, vitamin D serum content and cancer incidence or outcome has never been established, however. Although several epidemiologic studies demonstrated increased risk of colorectal, prostate, and breast cancers with low serum vitamin D levels, it is not known if the link is causative or associative. A series of studies regarding this issue was published in 2010 by the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers (VDPP), involving 10 cohorts (2588 female and 2135 male) to address the association between vitamin D and cancer.^{3,33–38} The VDPP examined the associations between serum or plasma 25(OH) vitamin D concentrations and the development of 7 types of rarer cancer: endometrial, esophageal, gastric, kidney, non-Hodgkin lymphoma, ovarian, and pancreatic cancers. Those studies failed to find a reduced risk of cancer incidence associated with higher levels > 30 ng/ml of serum 25(OH) vitamin D for these several types of cancers. In contrast, a study conducted using Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort, showed that men with lower 25(OH) vitamin D serum concentrations were at increased risk of bladder cancer compared with men with higher serum levels.³⁹ This observation is consistent with preclinical data in bladder cancer suggesting that exposure to vitamin D

(calcitriol) has anticancer properties.⁴⁰ Furthermore, higher serum 25(OH) vitamin D may be associated with higher concentration of vitamin D metabolites in the bladder.^{41,42} Consequently, increased exposure of the bladder tissue to these metabolites could promote apoptosis and differentiation and, therefore, reduce neoplastic processes in the bladder epithelium.

Vitamin D and cancer

There is evidence dating back to preclinical studies in the 1980s indicating that vitamin D compounds have anticancer activities.^{43–45} Since these initial studies, substantial preclinical evidence from in vitro and animal model studies suggest that a biologically active metabolites or analogs of vitamin D may play a critical role in cancer etiology and progression through anti-proliferative, pro-apoptotic, pro-differentiating, and anti-angiogenic mechanisms.^{5,46,47} A number of clinical studies have attempted to assess the efficacy of vitamin D, and its metabolites and analogs in the prevention and treatment of various malignancies including breast, prostate, and liver cancer, among others. Clinical studies have used vitamin D3 and calcitriol alone or in combination with cytotoxic agents. Most clinical trials involving vitamin D and its metabolites have been conducted in prostate cancer patients.^{48–60}

The biologic actions of vitamin D are attributed to its most active metabolite, calcitriol. Calcitriol was approved by the FDA for the treatment of chronic kidney disease, or hypoparathyroidism in patients with chronically low calcium levels. Since then, properties of calcitriol have been assessed in clinical studies of patients with different malignancies. Most preclinical data suggest that the optimal anti-tumor effect of calcitriol and other analogs is seen with the administration of high dose calcitriol on an intermittent schedule. Two pharmaceutical formulations of calcitriol are available – oral (Rocaltrol®, Roche Pharmaceutical Corporation) and intravenous (Calcijex®, Abbott Laboratories) – though neither is fully suited for anticancer treatment. Muindi et al have shown that Rocaltrol® was unsuitable for high dose administration because of inconvenience (maximum tolerated dose was not achieved even at doses that required patients to take ~ 80 caplets daily for 3 days each week) and lack of proportional increase in the serum levels and systemic exposure.⁶¹ Similar findings have also been reported by Beer and colleagues who observed “saturable absorption” at doses above 0.48 µg/kg.⁶²

A small number of single agent trials utilizing vitamin D3 and 1,25 hydroxyvitamin D have been conducted with limited success. The first clinical studies to evaluate the anti-proliferative and pro-differentiating properties of calcitriol were conducted in the early 1990's in myelodysplastic syndrome (MDS) and acute leukemia (AML) patients.^{63–66} A regimen of cytarabine and daily calcitriol prolonged remission in elderly patients with both diseases. Although some positive responses were observed in these trials, they were also associated with hypercalcemia in 10–30% of patients. Thus, early attempts at translating experimental vitamin D data to the clinic were not entirely successful, most likely due to the fact that the calcitriol dose employed was optimized for renal osteodystrophy and osteoporosis patients, and the treatment was not evaluated from the standpoint of the anticancer activity of the agent. Nonetheless, these early clinical findings precipitated

development of vitamin D analogs with modified chemical structures, in the hope of alleviating hypercalcemia and increasing the anticancer properties of calcitriol.^{67,68}

Vitamin D3 (cholecalciferol) in clinical trials

The observation that 1 alpha hydroxylase (the enzyme involved in hydroxylation of the calcitriol precursor) is present in malignant and normal tissues suggests that most cells in the body are able to synthesize calcitriol if levels of circulating 25 hydroxyvitamin D (cholecalciferol) are high enough.^{69–72} This has led to trials of vitamin D3 in healthy and cancer patients to prevent and treat cancer, respectively. A Women's Health Initiative trial of 400 IU of vitamin D and calcium, primarily to prevent fractures, showed that women concurrently treated with estrogen therapy had a decreased risk of colorectal cancer.⁷³ Although cancer was not a primary endpoint, this observation supports cancer protective properties of vitamin D even at small doses. In another study, conducted in prostate cancer patients, Woo et al investigated the effect of cholecalciferol on PSA levels and the rate of rise of PSA in these patients. Fifteen patients were treated with 2000 IU of vitamin D3 per day and monitored every 2–3 months. The PSA levels stabilized or decreased in nine patients for 21 months. Overall, PSA doubling time increased from 14.3 months to 25 months in patients treated with cholecalciferol and no side effects were reported.⁷⁴

To investigate the role of cholecalciferol in metastatic breast cancer patients Amir et al used a high dose of 10 000 IU of cholecalciferol per day for four months.⁷⁵ Palliative responses were assessed in 40 patients and a significant decrease in the sites of pain was recorded. However, there also was a significant increase in circulating calcium. Although patients did not experience cholecalciferol direct toxicity, no objective responses and clear increase in survival of this regimen was noted.

Calcitriol – clinical trials – single agent studies

Calcitriol has been used in a number of clinical trials, both as a single drug and in combination with chemotherapeutic agents. Based on data from preclinical studies, the anticancer activity of calcitriol requires supraphysiological doses and systemic exposure and before or simultaneous with cytotoxic drug administration. This requires careful development of appropriate dose/schedules of calcitriol and chemotherapy, as well as definition of toxicity and the maximum tolerated dose (MTD) or optimal biologic dose (OBD).

Based on laboratory data, high concentrations of calcitriol that elicit anti-tumor actions are safe and rarely cause limiting toxicity; the safety of intermittent very high dose calcitriol has been confirmed in cancer patients.^{10,11,15,56} No grade 3 or 4 toxicities have been seen in cancer patients when high dose calcitriol is administered intermittently. However, the current available formulations of calcitriol are not ideal for anti-tumor treatment since it is difficult to achieve systemic stable levels of the drug.^{56,62} After initial clinical trials in leukemic patients, calcitriol has been thought of as a toxic agent that induces unmanageable hypercalcemia, which has proven to be another impediment to its clinical application. However, this was not really the case, even in the trials in leukemia. Mild – moderate, rapidly reversible hypercalcemia has been seen with high dose intermittent as well as

continuous calcitriol regimens. However, clinical consequences of these changes in calcium level have not been seen. Oral administration of calcitriol on a daily schedule in prostate cancer patients proved that the agent could safely be administered for several months (up to 15 months) without causing dose-limiting hypercalcemia.⁴⁹

A phase I trial of calcitriol in patients with advanced malignancies was one of the first clinical studies conducted to determine the MTD of calcitriol as a single agent. Thirty-six patients were entered at doses ranging from 2 to 10 µg.⁷⁶ Calcitriol was administered by subcutaneous injection every other day. Pharmacokinetic evaluation revealed that serum calcitriol levels were maintained at near peak concentrations for at least 8 h following injection. This study showed that substantial doses of calcitriol can be administered via this route with tolerable toxicity. Another phase I study conducted by Beer and colleagues used a dose-escalating regimen of calcitriol. The agent was administered orally once per week for twenty cycles and no limiting toxicity was observed at doses up to 2.8 µg per kilogram weekly. However, the trial was terminated when incomplete and unreliable oral absorption at the dose 2.4 µg per kilogram and higher became apparent.⁶²

Beer et al treated 22 patients for a median of ten months with 0.5 µg/kg of calcitriol.⁴⁸ Their study showed that a weekly high dose did not cause significant toxicity and was safe in patients with a rising PSA after prostatectomy. Although the primary endpoint of the study, 50% reduction in the serum PSA, was not achieved, the study did show that a weekly regimen is effective in achieving plasma concentrations > 1 nM; this concentration, based on *in vivo* studies is higher than the minimum needed for calcitriol anti-tumor activity. Furthermore, this study proved that long-term calcitriol therapy was well tolerated by patients and did not cause limiting (> grade three) toxicity.

When 2–2.5 µg of calcitriol was given to prostate cancer patients daily there was a decrease in the rise of serum PSA or stabilization of PSA levels in those patients, suggesting slower progression of the disease upon calcitriol exposure.⁴⁹ However, urinary calcium increased and the authors were concerned that the risk of developing renal stones may be higher, and could outweigh the modest benefits of the calcitriol treatment.⁴⁹ To reduce the risk of hypercalciuria and avert renal toxicity and also potentially to achieve better efficacy of calcitriol, some groups employed intermittent administration of very high doses once or three times a week.^{48,50,77} This approach caused transient and short-term hypercalcemia, there was no clearly increased risk of renal stones or any other limiting toxicity. Substantially higher serum concentrations of calcitriol were also recorded, which would be expected to increase the potential for anti-tumor effects.

Although oral administration of high doses of calcitriol is safe, our group and that of Beer have shown that the pharmacokinetics of the commercially available oral formulations does not lead to a proportional increase in serum levels or predictable and maximal systemic exposure.^{56,61} This formulation is not therefore suitable for achieving high enough serum concentrations to elicit anticancer properties. Following these findings an improved oral formulation of calcitriol – DN-101 – was developed by Novacea Pharmaceuticals. A phase I study in patients with advanced malignancies was conducted to assess the safety of the new formulation of calcitriol.^{52,78} Pharmacokinetics of DN-101 showed that there was a linear

relationship between the dose and AUC. A dose of 165 mcg on week one followed by 45 mcg did not produce limiting toxicity. This formulation was then developed in men with prostate cancer in combination with docetaxel.

Calcitriol combination studies

Preclinical studies in cell and animal models have shown that calcitriol can interact in either a synergistic or additive manner with other chemotherapeutics.^{79–83} These findings support the development of combination therapy trials. Phase I and phase II studies involving calcitriol with docetaxel, gefitinib, paclitaxel, and carboplatin in advanced malignancies patients have been completed.^{54,55,84,85} Beer et al. conducted a combination calcitriol and docetaxel phase I and II clinical trials in patients with castration-resistant prostate cancer. The study evaluated weekly administration of 0.5 µg/kg calcitriol orally on day one followed by 36 mg/m² docetaxel intravenously on day two, and the cycles were repeated for six consecutive weeks. Five patients who had completed all calcitriol/docetaxel cycles achieved PSA reductions of > 50%. The treatment was well tolerated and only one patient experienced reversible, grade three toxicity.⁸⁶ Similar promising results were seen in another phase II trial, conducted by the same group, in a larger cohort of prostate cancer patients (37 patients). Beer et al sought to determine the safety and efficacy of weekly high dose oral calcitriol (Rocaltrol®) and docetaxel in patients with metastatic prostate cancer.⁸⁵ The group found that the combination of weekly oral high dose calcitriol and weekly docetaxel is a well-tolerated regimen for prostate cancer patients. Furthermore, the anti-tumor effect as assessed by 50% reduction in PSA, was substantially higher (81%) than would have been expected with weekly docetaxel alone.⁸⁵ However, the calcitriol formulation (Rocaltrol®) that was used in these studies is pharmaceutically and pharmacokinetically unattractive, as noted above.

Non-cytotoxic drugs have also been used in combination with calcitriol. Glucocorticoids such as dexamethasone ameliorate calcitriol-induced hypercalcemia which allows for a higher dose regimen.⁵³ Additionally, in preclinical studies, dexamethasone substantially enhances calcitriol anti-tumor activity. To examine this combination, Trump and colleagues conducted a phase II study of intravenous calcitriol at a dose of 74 µg weekly and dexamethasone in patients with castration-resistant prostate cancer.⁵³ While anti-tumor activity was noted as evidenced by PSA decreases in and long-term progression free survival of up to 3 years was seen, the level of activity in unselected patients was not sufficient to justify further exploration of this regimen. Calcitriol enhances the anti-tumor activities of several cytotoxic or differentiating agents. Fakih and colleagues conducted a phase I clinical study to determine the MTD of intravenously administered calcitriol in combination with dexamethasone and the EGFR antagonist, gefitinib (Iressa®).⁵⁵ Although the primary aim of the study was to establish the MTD of this combination treatment, a secondary objective was to examine the pharmacokinetic profile of intravenous calcitriol. The MTD was 125 µg/week calcitriol and the study found that the mean peak serum calcitriol concentration was 11.17 ng/ml and AUC was 54.89 ng h/ml; these are concentrations that are associated with anti-tumor activity in *in vivo* studies. In a second stage of this trial, simultaneously administered dexamethasone increased the MTD of calcitriol (120 mcg weekly).

These preclinical studies of combinations of cytotoxics and calcitriol provide support for the continued investigation of such combinations. Platinum analogs, taxanes, and DNA-intercalating agents are all potentiated by calcitriol, but only when administered before or during cytotoxic treatment.^{87,88}

ASCENT-1 trial

The commercially available calcitriol formulations are not suitable for use in cancer chemotherapy. A new oral formulation of calcitriol for cancer treatment was developed by Novacea. DN-101 was an oral high concentration formulation of calcitriol that was available in 15 and 45 µg caplets. This formulation demonstrated linear pharmacokinetics and dose-proportional pharmacokinetic relationship between C_{max} and AUC at doses up to 165 µg. DN-101 safety and pharmacokinetics were evaluated in a phase I clinical study.^{52,78} Based on the development of grade 2 hypercalcemia in two out of seven patients, the phase I study of DN-101 declared the maximal tolerated dose to be 60 µg per week. Subsequently, in what was called a phase II trial, a placebo-controlled study called ASCENT-1, was conducted which tested weekly calcitriol (45 µg) or placebo in combination treatment with docetaxel (36 mg/m² weekly for 3 out of 4 weeks) in prostate cancer patients with disease progressing despite androgen deprivation.⁵³ 250 men with metastatic, castration-resistant prostate cancer were randomly assigned to the placebo + docetaxel or calcitriol + docetaxel. The primary endpoint of the study was frequency of a 50% reduction of PSA within six months of starting the treatment. While PSA response was not significantly different, placebo (52%) vs. calcitriol (63%), patients in the DN-101 arm (calcitriol) had improved survival (24.5 months) when compared to the placebo arm (16.4 months). In addition to improved survival in the DN-101 and docetaxel group, adverse events were reduced. While this positive clinical outcome was very encouraging, this trial was not designed to delineate a difference in survival between these two treatments. No difference in PSA response was noted. A larger phase III study to determine if survival was improved was initiated.⁶⁰

ASCENT-2 trial

The randomized ASCENT II trial was conducted using the same high dose of calcitriol in combination with docetaxel in patients with progressive castration-resistant prostate cancer.⁶⁰ The primary objective of the trial was duration of survival; secondary endpoints included rates of thromboembolic events, gastrointestinal events, and overall serious adverse events, all events that seemed reduced in ASCENT-1. Patients were randomly assigned in a double blind fashion to two arms of the study. The experimental arm was identical to that employed in ASCENT 1 (28-day dosing cycle of 45 µg DN-101 on days 1, 8, and 15; 36 mg/m² docetaxel on days 2, 9, and 16; and 8 mg oral dexamethasone). However, when the ASCENT-2 trial was initiated the FDA-approved standard regimen for docetaxel in men with castration-resistant prostate cancer was 75 mg/m² administered every-3-weeks. In a prospective randomized trial docetaxel 75 mg/m² every 3 weeks was superior to 36 mg/m² weekly 3 weeks out of 4 [median survival 18.9mo vs. 17.4mo, respectively].⁸⁹ Therefore this standard therapy of every-3-weeks was chosen as the control arm of ASCENT-2 combined with placebo and was compared to weekly docetaxel plus calcitriol.

Interim analysis by the Data Safety Monitoring Board for this study showed inferior survival in the experimental arm and the study was halted. At the point of terminating the study there were 953 patients enrolled in the trial.⁶⁰ Median overall survival in the ASCENT arm was 17.8 months and 20.2 months in the control arm ($P = .002$).

The inferior survival in the calcitriol arm was surprising. While this result may stem from the lack of activity of calcitriol in potentiating docetaxel in men with castration-resistant prostate cancer at least two other concerns must be considered:

1. Since weekly docetaxel has been proven to be inferior to every-3-weeks docetaxel, the failure of the experimental arm in this study was clearly confounded by the inferiority of the docetaxel regimen.
2. Another factor that must be considered in evaluating this study is the lack of convincing data that this calcitriol dose and regimen is optimal or appropriate. The dose employed was ~ 1/3 of the MTD of intermittent calcitriol. Therefore, one must wonder whether the failure of this trial was influenced by the dose of calcitriol employed.

Notably, both arms had the same rates of total adverse effects, but the number of deaths was significantly higher in the ASCENT arm (17%) when compared to the control arm (10.1%). The majority of early deaths were caused by progressive prostate cancer. Previously seen protective benefits of calcitriol with regard to serious adverse effects were not confirmed in the ASCENT-2 trial. There is no clear explanation as to why survival was lower in the treatment arm in ASCENT-1 vs. ASCENT-2 since regimens in calcitriol arm were identical.

Vitamin D analogs

Due to the potential of calcitriol to cause hypercalcemia and in order to improve on the anticancer effects of this compound, attempts have been made to develop more effective and less toxic analogs of vitamin D. In some cases preclinical studies suggested the usefulness of new analogs, and several clinical studies have been conducted using these agents.^{90–92} Seocalcitol (EB1089) has been studied in phase I and II trials.

A phase I study was conducted in patients with advanced breast and colorectal cancers to assess the pharmacokinetic profile and toxicity of seocalcitol. While disease stabilization was noted in six patients for three months there were no other anti-tumor effects in that group of patients.⁹⁰ The oral dose that led to hypercalciuria was considered dose-limiting toxicity and was subsequently used in the phase II study of the agent. These studies did not provide data that would support anti-tumor activity of seocalcitol on this dose and schedule in pancreatic or hepatocellular carcinoma patients.^{91,92}

A phase I/II study of 19-nor-1alpha-25-dihydroxyvitamin D₂ (paricalcitol) in advanced prostate cancer patients was conducted by Schwartz et al to assess the safety and efficacy of this vitamin D analog.⁹³ The primary endpoint in this study was PSA response. Although the drug was generally well tolerated by patients at intravenous doses 3–15 µg/m² three times weekly, no significant response was recorded.⁹⁴

Most analogs tend to cause less hypercalcemia than calcitriol, but they also have a lower affinity for the vitamin D receptor, which in turn has been associated with reduction of anticancer properties.⁵

Conclusions

Several lines of evidence support the hypothesis that vitamin D and its metabolites might be beneficial to cancer chemoprevention and therapy. This relationship has been established based on *in vitro* and *in vivo* studies in tumor cells and animal models of different types of cancer, respectively. Many groups, including ours, have shown that high concentrations of biologically active vitamin D metabolites inhibit cancer cell proliferation and can induce differentiation in some situations. The link between vitamin D and decreased incidence in several malignancies has also been strongly supported by epidemiologic studies.

Populations that are less likely to synthesize vitamin D based on their geographical location (due to lower levels of ultraviolet radiation) show higher risk of certain malignancies. This suggests that vitamin D provides protective effects against some malignancies. There are several serious limitations of testing calcitriol and other vitamin D metabolites in cancer prevention and treatment. It remains to be determined what the optimal biologic dose or concentration of calcitriol are. Second, most clinical studies did not use the optimal dose. Finally, due to drug formulation and other factors, clinical trials have not been designed adequately to assess the efficacy of calcitriol and analogs. Although results from preclinical studies strongly confirm anti-tumor properties of calcitriol, the lack of properly designed regimens has generated doubts about its clinical usefulness.

A number of clinical studies have been conducted with calcitriol or its analogs, but all are hampered by the above considerations. Many early studies of calcitriol and analogs employed daily, relatively low dose regimens. Little to no anti-tumor effects of limiting or at least worrisome hypercalcemia were seen. Our group and others have demonstrated that calcitriol exposure (AUC, C_{max}) comparable to that achieved pre-clinically and which clearly results in anti-tumor effects is achieved with a high dose intermittent regimen. Results from clinical and preclinical studies show that high doses of calcitriol can be administered safely alone or in combination with other agents to elicit or enhance anti-tumor activity. Therefore, the rigorous testing of the anti-tumor effects of calcitriol should employ a high dose intermittent regimen of the dose approximately the MTD 100–120 $\mu\text{g}/\text{m}^2$. No trials to date have used the MTD. Other dosing schedules, molecular endpoints, and interactions with other anticancer agents have not been thoroughly investigated.

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Practice points

- Vitamin D deficiency/insufficiency are associated with increased cancer risk and poor outcome
- Prospective trials to evaluate the effect of correcting deficiency/insufficiency are needed
- High dose calcitriol is safe if used on an intermittent schedule

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Research agenda

- Develop appropriate formulations of calcitriol for clinical use
- Evaluate this formulation in a rigorous clinical development plan
 - Which cancer(s)
 - What clinical settings
 - With which chemotherapy regimens
- Evaluate other analogs and determine the biologically optimal dose and schedule

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