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PROSTATE CANCER: THE ROLES OF VITAMIN D DEFICIECNY

Emmanuel Ifeanyi Obeagu*[1], Frances Ugonne Ogunnaya[2], Getrude Uzoma Obeagu[3] and Calista Ndidi Adike[4]

[1]Department of Medical Laboratory Science, Kampala International University, Uganda.
[2]Department of Internal Medicine, Newark Beth Israel Medical Center, 201 Lyons Avenue, Newark NJ.
[3]School of Nursing Science, Kampala International University, Uganda.
[4]Department of Medical Laboratory Science, Nnamdi Azikiwe University, Nnewi Campus, Nnewi, Anambra State, Nigeria.

***Corresponding Author: Emmanuel Ifeanyi Obeagu**

Department of Medical Laboratory Science, Kampala International University, Uganda.

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ABSTRACT

Since the early 1970s, scientists have wondered whether vitamin D compounds might play a role in both cancer development and treatment. Vitamin D receptors (VDRs) have been found in human cancer cells and in vitro growth arrest has been observed in response to treatment with vitamin D compounds. Due to the presence of vitamin D receptors in most human tissues and cancers that develop from these tissues. Numerous epidemiologic studies linking vitamin D to prostate cancer risk and outcome are one reason to investigate vitamin D`s role in the disease. African-American men's studies provide one of the strongest arguments in favor of a link between vitamin D and prostate cancer. When compared to Caucasian men, these men have significantly higher rates of prostate cancer mortality and low 25(OH)D3 levels (primarily as a result of the effect of skin pigmentation reducing intracutaneous synthesis of vitamin D).One might anticipate that different isoforms of vitamin D-metabolizing genes and possibly even vitamin D-binding protein may be connected with various cancer risks or outcomes if it were the case that low serum levels of 25(OH)D3 increased the risk of prostate and other cancers. Although there is a strong correlation between polymorphisms in the genes that control the production of vitamin D and vitamin D serum levels, a connection between these polymorphisms and prostate cancer risk or prognosis is still difficult to find.

KEYWORDS: *inflammation, prostate cancer, vitamin D.*

INTRODUCTION

Since the early 1970s, scientists have wondered whether vitamin D compounds may play a part in both the development and treatment of cancer. Vitamin D receptor (VDR) was found in human cancer cells, and growth arrest in vitro was observed in response to treatment with vitamin D compounds.[1-3] This treatment was used in a hamster model of carcinogen-induced cancer, which demonstrated that it could prevent the development of cancer. In this paper, we aim to summarize the research on vitamin D and prostate cancer. However, given the widespread expression of VDR as well as the enzymes[4-8] There is strong evidence that vitamin D signaling may be involved in the genesis, course, and treatment of other types of cancer due to the presence of vitamin D receptors (e.g., CYP 24a1, CYP 27b1) in nearly all human tissues and cancers that develop from those tissues.[1-3]

EPIDEMIOLOGIC STUDIES OF VITAMIN D IN PROSTATE CANCER

Numerous epidemiologic studies linking vitamin D to prostate cancer risk and outcome are one reason to investigate vitamin D's role in the disease. Similar to the situation in many other tumors (e. g. studies have shown a higher risk of prostate cancer or deadly prostate cancer in men living in Northern latitudes, as well as a higher overall prostate cancer risk and/or poor prognosis among men whose estimated vitamin D intake is low or in whom 25(OH)D3 has been measured. African-American men's studies provide one of the strongest arguments in favor of a link between vitamin D and prostate cancer. When compared to Caucasian men, these men have significantly higher rates of prostate cancer mortality and low 25(OH)D3 levels (primarily as a result of the effect of skin pigmentation reducing intracutaneous synthesis of vitamin D). Despite numerous descriptions of this relationship, it is still unknown how it came to be. Disparities in access to medical care are unquestionably a factor in the unfavorable results among African-American men. One might anticipate that different isoforms of vitamin D-metabolizing genes and possibly even vitamin D-binding protein may be connected with various cancer risks or outcomes if it were the case that low serum levels of 25(OH)D3 increased the risk of prostate and other cancers. Although there is a strong

correlation between polymorphisms in the genes that control the production of vitamin D and vitamin D serum levels, a connection between these polymorphisms and prostate cancer risk or prognosis is still difficult to find. Important details about the relationship between vitamin D supplementation and the risk of cancer and cardiovascular disease are provided by the VITAL study (vitamin D and omega-3 trial), a randomized trial involving 20 000 adults aged 55 or older who received either 2000 IU of vitamin D3 or omega-3 fatty acids, or both, or a placebo. 5 There are only two "large" trials in which participants receive a dose of vitamin D that is likely to increase the 25(OH)D3 level in the majority of patients, and this one stands out for two crucial reasons: (1) the accrual objective is sufficient to make it likely that the effects of supplementation will be able to be determined with substantial statistical power; and (2) it is a very important trial. The trial's findings will significantly contribute to elucidating the impact of vitamin D supplementation on health outcomes.[8]

ANALOGS OF $1,25(OH)_2D$

Considerable work has been done seeking to delineate analogs of $1,25(OH)_2D$ that may have greater antitumor activity and/or less potential to induce hypercalcemia, the only known toxic effect of vitamin D compounds. The analogs EB 1089, MC903, 22-oxacalcitriol, BGP-13(a 24-chloro calcipotriene-based D_3 analog), R024-2637, 19-nor-14-epi-23-yne-$1,25(OH)_2D_3$ (TX 522, inecalcitol), and 19-nor-14,20-bisepi-23-yne-$1,25(OH)_2D_3$ (TX 527) are reported to be less likely to cause hypercalcemia than the parent compound calcitriol. Each of these analogs appears to have activity in preclinical prostate cancer models.[9-12]

A safe dose of inecalcitol (TX 522) has been established (4000 mcg daily [QD]), and a Phase II trial combining it with docetaxel suggests that this combination is superior to docetaxel alone. But no conclusive trial has been conducted (48, 49). Though conceptually appealing, 1,25(OH)2D3 analogs have not been thoroughly studied to demonstrate that they have antitumor activity superior to 1,25(OH)2D3 at equitoxic doses, or that they have a lower risk of hypercalcemia when administered at 1,25(OH)2D3's "equi-effective" antitumor doses. Differences in protein binding and catabolism between analogs and the parent compound can be used to explain a large portion of the apparent reduction in the potential to cause hypercalcemia for many analogs. The intracellular half-life of an analog will be prolonged, for instance, by "resistance" to CYP24A1 breakdown. A given concentration of an analog would be "more potent" if it were resistant to CYP24A1-mediated catabolism because intracellular removal would take longer. At a molecularly equivalent dose of 1,25(OH)2D3, such substances would most likely result in more hypercalcemia. The active moiety of a drug is the portion that is "free" and physiologically active in tissues, so if an analog is more tightly protein bound, it will require a higher dose of that analog to cause hypercalcemia in an intact animal. The fact that a dose of an analog that causes hypercalcemia is higher than a dose of calcitriol that causes hypercalcemia does not prove that the analog is inherently "less hypercalcemic.". Ma and colleagues have shown that the maximum tolerable doses of inecalcitol and calcitriol differ in mice, and that inecalcitol's antitumor effects were observed at lower concentrations of this agent than calcitriol. However, doses of these two substances that led to comparable levels of hypercalcemia also had comparable antitumor effects in a xenograft model of squamous cell carcinoma. No vitamin D analog has been created that can clearly distinguish between the agent's hypercalcemic effects and its anticancer or other biological effects.[13]

RESISTANCE TO THE ANTITUMOR EFFECTS OF VITAMIN D ANALOGS

The clinical activity of 1,25(OH)2D3 and analogs has proven to be much more challenging to prove than might be anticipated given the breadth of preclinical data indicating significant anticancer effects, as will be discussed below. Existence of significant "resistance" mechanisms that might impede clinical trials is one factor that might be responsible for this. Numerous in vitro and in vivo preclinical models have shown resistance to the antiproliferative effects of vitamin D analogs. Loss or reduced function of VDR and increased CYP24A1-mediated catabolism are the two most well-known mechanisms of resistance to vitamin D compounds. It is obvious that diminished responsiveness to vitamin D analogs in vivo and in vitro is associated with the absence or reduced expression of the VDR. Variations in cofactor concentrations necessary for vitamin D signaling as well as polymorphisms in the VDR structure may affect how sensitive tumor cells are to 1,25(OH)2D3. In a similar vein, administration of a proteasome inhibitor, which prevents intracellular protein degradation, boosts the intracellular content of VDR and intensifies the antitumor effects of calcitriol in a bone tumor cell line when administered in vitro.[14-15]

In vitro, in vivo, and possibly in the clinic, modifications in CYP24A1 activity have been shown to modulate the antitumor effect of 1,25(OH)2D3 and analogs. Few studies have been conducted looking to combine such inhibitors and vitamin D compounds as therapy for cancer. However, several classes of CYP24A1 inhibitors have been developed and preclinical activity demonstrated.[16-18]

COMBINATION THERAPIES WITH VITAMIN D COMPOUNDS

Although 1,25(OH)2D3 compounds have demonstrated promising activity in preclinical models, single agents typically have a limited impact on clinical cancer therapy. Combination therapies based on 1,25(OH)2D3 compounds are being investigated to improve antitumor effectiveness.

The glucocorticoids

The interaction of glucocorticoids with vitamin D was one of the first substances to be studied. Glucocorticoids effectively lower hypercalcemia brought on by vitamin D and have direct anticancer effects on their own. In numerous cell types, glucocorticoids increase the expression of VDR. With different tissue types, tumor types, and species, this occurs to varying degrees. Preclinical studies show that calcitriol and glucocorticoids have synergistic antitumor effects in human prostate cancer xenografts, and dexamethasone's ability to prevent calcitriol-induced hypercalcemia led to the inclusion of dexamethasone in many clinical trials along with calcitriol.[19]

Agents that block CYP24A1

General (e.g, ketoconazole) P450 inhibitors inhibit CYP24A1 activity while enhancing the antitumor effects of liarazole and calcitriol. Specific inhibitors like progesterone, natural products like soy or its component isoflavones like genistein and daidzein, and secosteroid derivatives of 1,25(OH)2D all inhibit CYP24A1 (directly or indirectly) and enhance the antitumor effects of vitamin D compounds.[20] The combination of calcitriol and genistein, which both competitively inhibit CYP24a1 activity, inhibits tumor growth in human prostate models. Ketoconazole amplifies the antitumor effect of high dose, intermittently administered calcitriol, as demonstrated by Muindi and colleagues in a prostate cancer model (PC-3).[21]

NSAIDS, or nonsteroidal anti-inflammatory drugs

As mentioned above, blocking the production of prostaglandins may enhance the effects of vitamin D compounds. In a Phase II trial, naproxen, a nonselective NSAID, was combined with high doses of calcitriol in patients with early recurrent prostate cancer. The results showed some benefits in terms of a slower doubling time for PSA.[22]

The retinoids

Given the interaction between 1,25(OH)2D3-VDR and retinoid X receptor (RXR)-9-cisretinoic acid, it is conceivable to speculate that ligands for the retinoid receptors, retinoic acid receptors (RARs), and RXRs would modify 1,25(OH)2D3 action. Numerous studies show that retinoid compounds can enhance the antitumor effects of calcitriol.[23]

Substances that are cytotoxic

Numerous anticancer medications, including doxorubicin, mitoxantrone, etoposide, and topoisomerase inhibitors such as irinotecan, camptosar, and etoposide, as well as in vitro and in vivo studies have shown that vitamin D compounds increase the cytotoxicity of many of these medications. The effects of this interaction include enhanced induction of apoptosis, increased expression of p73point, increased expression of p21, and perturbation of cell cycle kinetics. These effects are most pronounced when vitamin D compounds are given either before or at the same time as the cytotoxic agent.[24-26]

Ionizing radiation and photodynamic therapy

Ionizing radiation and photodynamic therapy both have antitumor effects that are enhanced by vitamin D compounds. There hasn't been much clinical research into this potentially beneficial combination.[27]

Single-agent vitamin D compounds

Patients with castration-resistant prostate cancer (CRPC) and castration-sensitive disease have undergone single agent evaluations with calcitriol, 1-hydroxyvitamin D2 (doxercalciferol), and 19-nor-1alpha-25-dihydroxyvitamin D2 (paricalcitol). Although there is a decrease in the rate of PSA rise in the castration-sensitive setting and some evidence of activity in CRPC (19 percent PSA response rate),[28] none of these studies offer convincing evidence of clinically significant single-agent activity of calcitriol. The fact that calcitriol is typically used in combination with glucocorticoids has complicated analyses of its single-agent activity. This was done to allow for the safest possible dosage of calcitriol because studies have shown that glucocorticoids can interfere with calcitriol's ability to cause hypercalcemia. Calculating the calcitriol response rate in single-arm studies using calcitriol + dexamethasone is challenging because glucocorticoids have anticancer activity in men with prostate cancer. PSA response rates have been reported in the range of 3 percent to 10% in large trials where single-agent glucocorticoids were tested as the control arm. Based on these findings, one might say that a PSA response rate of 19% after calcitriol po + dexamethasone is "interesting. However, rates of 25–45 percent are reported in numerous small studies that focus only on glucocorticoids.[29] Despite the fact that all of the patients were castration resistant, the small number of patients who were enrolled in many trials, the variability in prior treatments, and the extent of the disease are all contributing factors to the wide variation in PSA response to glucocorticoids. There are interesting data suggesting that response rates to various glucocorticoids may vary. But in general, the data show a response rate to calcitriol + dexamethasone that is hard to distinguish from the rate one might anticipate with dexamethasone alone.

CONCLUSION

The significance of vitamin D signaling in prostate cancer is well supported by a wealth of data. Using vitamin D alone or in combination with other antineoplastic agents, it is possible to treat cancers that have already spread. If these biological observations can be used to inform prevention tactics, careful studies of vitamin D supplementation will be necessary. The use of vitamin D compounds in the treatment of prostate cancer is, regrettably, not well understood.

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