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Vitamin D as potential therapeutic anticancer agent

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Abstract

The role of vitamin D is implicated in carcinogenesis through numerous biological processes like induction of apoptosis, modulation of immune system inhibition of inflammation and cell proliferation and promotion of cell differentiation. Its use as additional adjuvant drug with cancer treatment may be novel combination for improved outcome of different cancers. Numerous preclinical, epidemiological and clinical studies support the role of vitamin D as an anticancer agent. Anticancer properties of vitamin D have been studied widely (both in vivo and in vitro) among various cancers and found to have promising results.

There are considerable data that indicate synergistic potential of calcitriol and antitumor agents. Possible mechanisms for modulatory anticancer activity of vitamin D include its antiproliferative, prodifferentiating, and anti-angiogenic and apoptic properties. Calcitriol reduces invasiveness and metastatic potential of many cancer cells by inhibiting angiogenesis and regulating expression of the key molecules involved in invasion and metastasis. Anticancer activity of vitamin D is synergistic or additive with the antineoplastic actions of several drugs including cytotoxic chemotherapy agents like paclitaxel, docetaxel, platinum base compounds and mitoxantrone. Benefits of addition of vitamin D should be weighed against the risk of its toxicity.

Keywords: *calcitriol, antiproliferative, apoptosis, therapeutic agent*

Introduction

Vitamin D is a fat-soluble vitamin, referred as prohormone, metabolites and analogues of these substances. Major source of vitamin D is solar ultraviolet-B exposure. Calcitriol, an active form of vitamin D is synthesized in kidney. Its precursor undergoes hydroxylation in liver and kidneys to form 1,25dihydroxycholecalciferol. Now it has been observed that calcitriol is synthesized in several other tissues like breast, ovary, colon and prostate. Vitamin D binds to a nuclear receptor and modulates gene expression. Vitamin D receptors (VDR) are present in a wide variety of cells including malignant cells [1]. Calcitriol is the chief regulator of calcium homeostasis and bone metabolism. But in past few decades its multiple diversified effects have been identified throughout the human body.

The role of vitamin D is implicated in carcinogenesis through numerous biological processes like induction of apoptosis, modulation of immune system inhibition of inflammation and cell proliferation and promotion of cell differentiation [2]. Preclinical studies showed antitumor in vitro and in vivo effects of 1,25D3-an active metabolite of vitamin D and its analogues. In addition, its administration potentiates the effects of chemotherapeutic agents [3]. Several important anticancer mechanisms have been identified and the molecular mediators of calcitriol actions investigated by the researchers. Its use as additional adjuvant drug with cancer treatment may be novel combination for improved outcome of different cancers. Cancer treatment induced bone loss is one of adverse effect of treatment in breast and prostate cancer patients and those receive antiresorptive agents for skeletal metastasis. Such patients get benefited if their vitamin D levels remain within normal range [4].

Vitamin D as anticancer agent

ANumerous preclinical, epidemiological, and clinical studies support the role of vitamin D as an anticancer agent. Anticancer properties of vitamin D have been studied widely (both in vivo and in vitro) among various cancers and found to have promising results. Numerous ecological and epidemiological data revealed protective effect of regular exposure to sunlight against development of various types of cancers. Also administration of vitamin D results in regression and death of the malignant cells to some extent. Possible mechanisms for modulatory anticancer activity of vitamin D include its antiproliferative, prodifferentiating, and anti-angiogenic and apoptic properties [5]. In addition, it causes immunomodulation through multiple pathways to enhance immune tolerance. Calcitriol reduces invasiveness and metastatic potential of many cancer cells by inhibiting angiogenesis and regulating expression of the key molecules involved in invasion and metastasis [6]. Calcitriol and its analogues directly inhibit the proliferation of endothelial cells and tumor angiogenesis. In addition, they regulate expression of key factors of angiogenesis [7]. Role of chronic low-grade systemic inflammation has been implicated in the pathogenesis of cancer. Anti-inflammatory actions of vitamin D include suppression of prostaglandin actions, inhibition of p38 stress kinase and NF-kB signaling and subsequent production of proinflammatory cytokines [8]. Calcitriol controls the growth cells by modulation of expression and activity of key growth factors in

malignant cells. Up regulation of expression of insulinlike growth factors binding protein-3 (IGFBP-3) by calcitriol causes inhibition of cell proliferation by increasing the expression of p21 [9]. Apart from these antineoplastic actions, vitamin D also affects the energy utilization in cancer cells. It regulates metabolism-related tumor suppressor and oncogenes, energy and nutrient sensing pathways [10].

Vitamin D decreases expression of aromatase, an enzyme that catalyzes estrogen synthesis in breast cancer via direct repression of transcription and reduction of prostaglandin synthesis, which are chief stimulators of aromatase transcription. Vitamin D may modulate triple negative breast cancer by prevention of cathepsin L-mediated degradation of 53BP1. In BRCAA1 deficiency, increased degradation of 53BP1 facilitates unregulated growth of the cells that can be reversed by administration of vitamin D [11]. Anticancer activity of vitamin D is synergistic or additive with the antineoplastic actions of several drugs including cytotoxic chemotherapy agents like paclitaxel, docetaxel, platinum base compounds and mitoxantrone [12-15]. In some of the malignant cells, calcitriol induces differentiation in such a way that they acquire a more mature and less malignant phenotype. In addition, calcitriol induces apoptosis in some of cancer cells by different mechanism. In breast and prostate cancer, it activates intrinsic pathway of apoptosis leading to disruption of mitochondrial activities, release of cytochromes and free radicals. While in some cells, it enhances apoptosis in response to administration of chemotherapy and radiation therapy [16]. Androgen receptors (AR) mediate gonadal actions on prostate cancer cells. Calcitriol induces differentiation of prostate cell progenitor into AR positive luminal epithelial cells. In addition, it induces increase in androgen stimulated prostate-specific antigen [17-19]. In colon cancer, components of calcitriol pathway can modulate the unregulated wnt/B-catenin signaling pathway to increase E-cadherin and sequestration of B catenin at the membrane [20].

Dosage of vitamin D in cancer treatment

There is a lot of controversy about dosage of vitamin D for anticancer purpose. Most of the anticancer actions of vitamin D have been found with chronic administration at dose of 2000-4000IU/day. But this may lead to its toxicity, as it is lipid soluble vitamin that can be stored in adipose tissues. Because of calcium-mobilizing action, administration of vitamin D for prolonged duration causes hypercalcemia. Hypercalcemia is the principle toxicity that leads to the progression of atherosclerosis. Hence daily brief exposure of substantial are of skin to sunlight is the most preferred physiologic safe source of vitamin D. Such ultraviolet exposure is equivalent to daily oral intake of 10000 IU vitamin D3 [21]. Benefits of addition of vitamin D should be weighed against the risk of its toxicity. Hence, careful monitoring of cancer patients who are receiving vitamin D is recommended. To avoid hypercalcemia due to vitamin D toxicity, various analogues with low calcemic properties like EB1089 (seacalcitol), BXL0124, Inecalcitol and EM1 have been synthesized [2].

Calcitriol, the hormonal active form of vitamin D has been evaluated in clinical trials as a potential anti-cancer therapeutic agent. In animal models, there is evidence of multiple anti-cancer properties of vitamin D in malignant cells that halts the growth and progression of the tumors [8]. It is emerging as a promising adjuvant drug in various types of cancer therapy, hence raising the possibility of its use as anti-cancer agent. AIPC study of Calcitriol Enhancing Taxotere (ASCENT) trial was a double blind randomized phase II trial that evaluated efficacy and safety of DN-101 (high-dose calcitriol) orally once a week with weekly docetaxel among patients with metastatic adenocarcinoma of the prostate cancer with evidence of progression. Vitamin D in high dose enhanced efficacy of active drugs with statistically significant improvement in the overall survival and time to progression. However, it did not produce a statistically significant improvement in the PSA response rate [22]. In case of prostate cancer, calcitriol exhibits antineoplastic action by inducing cell cycle arrest and accumulation of cells in G0/G1 phase of cycle. In addition, it increases the expression of the cyclin-dependent kinase (CDK2) inhibitors [23].

With these concerns, anticancer properties of vitamin D are ray of hope to improve overall and disease free survival among cancer patients. There are considerable data that indicate synergistic potential of calcitriol and antitumor agents. Although technically it is hormone, it exerts anticancer effects through multiple mechanisms. In future, large population, based prospective studies are warranted to evaluate the role of vitamin D as therapeutic anticancer agent.

Conclusion

Calcitriol has been found to be associated with beneficial anticancer effects via multiple mechanisms. Cancer patients should be screened for deficiency of vitamin D and accordingly treat it to improve the prognosis of the disease. There are substantial evidences in preclinical and epidemiological studies that suggest utility of vitamin D as antineoplastic agent. It exerts synergistic or additive effect in combination with various types of cytotoxic agents in cancer treatment.

References

1. Krishnan AV, Trump DL, Johnson CS, Feldman D. The Role of Vitamin D in Cancer Prevention and Treatment. *Endocrinol Metab Clin North Am.* 2010; 39:401-418.
2. Duffy MJ, Murray A, Synnott NC, O'Donovan N, Crown J.Vitamin D analogues: Potential use in cancer treatment. *Crit Rev Oncol Hematol.* 2017; 112:190-197.
3. Ali MM, Vaidya V. Vitamin D and cancer. *J Can Res Ther.* 2007; 3:225-230.
4. Hadji P. Cancer Treatment-Induced Bone Loss in women with breast cancer. *Bone KEy Reports.* 2015; 4:692.
5. Chakraborti CK. Vitamin D as a promising anticancer agent. *Indian J Pharmacol.* 2011; 43:113-120.
6. Koli K, Keski-Oja J. 1alpha,25-dihydroxyvitamin D3 and its analogues down-regulate cell invasion-associated proteases in cultured malignant cells. *Cell Growth Differ.* 2000; 11:221-229.
7. Mantell DJ, Owens PE, Bundred NJ, Mawer EB, Canfield AE. 1 alpha,25-Dihydroxyvitamin D(3) inhibits angiogenesis in vitro and in vivo. *Circ Res.* 2000; 87:214-220.
8. Krishnan AV, Feldman D.Mechanisms of the anti-cancer and anti-inflammatory actions of vitamin D. *Annu Rev Pharmacol Toxicol*. 2011; 51:311-336.
9. Boyle BJ, Zhao XY, Cohen P, Feldman D. Insulin-like growth factor binding protein-3 mediates 1 alpha,25-dihydroxyvitamin d(3) growth inhibition in the LNCaP prostate cancer cell line through p21/WAF1. *J Urol.* 2001; 165:1319-1224.

10. Abu el MaatyMA, Stefan WölflS. Vitamin D as a Novel Regulator of TumorMetabolism: Insights on Potential Mechanismsand Implications for Anti-Cancer Therapy. *Int J Mol Sci.* 2017; 18: 2184.
11. Grotsky DA, Gonzalez-Suarez I, Novell A, Neumann MA, Yaddanapudi SC, et al. BRCA1 loss activates cathepsin L–mediated degradation of 53BP1 in breast cancer cells. *J Cell Biol.* 2013; 200:187-202.
12. Hershberger PA, Yu WD, Modzelewski RA, Rueger RM, Johnson CS, ett al. Calcitriol (1,25-dihydroxycholecalciferol) enhances paclitaxel antitumor activity in vitro and in vivo and accelerates paclitaxel-induced apoptosis. *Clin Cancer Res.* 2001; 7:1043-1051.
13. Beer TM, Hough KM, Garzotto M, Lowe BA, Henner WD. Weekly high-dose calcitriol and docetaxel in advanced prostate cancer. *Semin Oncol.* 2001; 28:49-55.
14. Moffatt KA, Johannes WU, Miller GJ.1α,25dihydroxyvitamin D and platinum drugs act synergistically to inhibit the growth of prostate cancer cell lines. *Clin Cancer Res.*1999; 5:695-703.
15. Ahmed S, Johnson CS, Rueger RM, Trump DL. Calcitriol (1,25-dihydroxycholecalciferol) potentiates activity of mitoxantrone/dexamethasone in an androgen independent prostate cancer model. *J Urol.* 2002; 168:756-761.
16. Ylikomi T, Laaksi I, Lou YR, Martikainen P, Miettinen S, et al. Antiproliferative action of vitamin D. *Vitam Horm.* 2002; 64:357-406.
17. Murthy S, Agoulnik IU, Weigel NL. Androgen receptor signaling and vitamin D receptor action in prostate cancer cells. *Prostate.* 2005; 64:362-372.
18. Liu G, Wilding G, Staab MJ, Horvath D, Miller K, et al. Phase II study of 1 alpha-hydroxyvitamin D(2) in the treatment of advanced androgen-independent prostate cancer. *Clin Cancer Res*. 2003; 9:4077-4083.
19. Schwartz GG, Hall MC, Stindt D, Patton S, Lovato J, Torti FM. Phase I/II study of 19-nor-1alpha-25-dihydroxyvitamin D2 (paricalcitol) in advanced, androgen-insensitive prostate cancer. *Clin Cancer Res.* 2005; 11:8680-8685.
20. Stubbins RE, Hakeem A, Nunez NP. Using components of the vitamin D pathway to prevent and treat colon cancer. *Nutr Rev.* 2012; 70:721-729.
21. Vieth R. Vitamin D and Cancer Mini-Symposium: The Risk of Additional Vitamin D. *Ann Epidemiol.* 19: 441-445.
22. Beer TM, Ryan CW, Venner PM, Petrylak DP, Chatta GS, et al. Double-Blinded Randomized Study of High-Dose Calcitriol Plus Docetaxel Compared With Placebo Plus Docetaxel in Androgen-Independent Prostate Cancer: A Report From the ASCENT Investigators. *J Clin Oncol.* 2007; 25:669-674.
23. Krishnan AV, Moreno J, Nonn L, Swami S, Peehl DM, et al. Calcitriol as a Chemopreventive and Therapeutic Agent in Prostate Cancer: Role of Anti-Inflammatory Activity. *J Bone Miner Res.* 2017; 22:V74-V80.

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