Review Article

Yasemin Benderli Cihan*

Does vitamin D prevent radiotherapy-induced toxicity?

D Vitamini Radyoterapi ile İndüklenmiş Toksisiteyi Engeller Mi?

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Abstract: Vitamin D is known as the bone hormone, it is also know that it has effects on cancer because of its anti-inflammatory and immunomodulatory characteristics and its effects on cytokine levels. It is seen that vitamin D use together with radiotherapy can have a positive effect on cancer treatment. It should be investigated whether toxicities due to radiation is prevented by vitamin D metabolites' increasing the induction of immunomodulator cells and the capacities of immune response cells. Use of 1,25[OH]2 Vitamin D3 analogs as an adjuvant immunomodulator for patients receiving radiotherapy should be evaluated. There is a need for studies to be done in this regard.

Keywords: Vitamin D; Radiotherapy; Toxicity.

Öz: D vitamini genel olarak kemik hormonu olarak bilinmesine rağmen, antienflamatuar ve immünmodülatör özellikleri ve sitokin seviyeleri üzerine olası etkileri nedeniyle kanser tedavisinde önemli etkileri olduğu bilinmektedir. D vitamininin radyoterapi ile birlikte kullanılmasının kanser tedavisinde olumlu etkisi olabileceği görülmektedir. Vitamin D metabolitlerinin immunomodulatör hücrelerin indüksiyonunu ve bağışıklık yanıt hücrelerinin kapasitelerini arttırmasıyla radyasyonun neden olduğu toksisitelerin önüne geçilip geçilmeyeceği araştırılmalıdır. Özellikle, 1,25(OH)2 Vitamin D3 analogların, radyoterapi uygulanılan hastalarda bir adjuvan immunomodulatuar olarak kullanılması değerlendirilmelidir. Bu konuda yapılacak çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: D vitamini; radyoterapi; toksisite.

Introduction

Vitamin D, which has an important role in human health, is a fat soluble vitamin. Since 1,25-dihydroxy vitamin D [1,25[OH]2D], which is the active metabolite of vitamin D, is similar to steroid hormones structurally and functionally, it is evaluated as a hormone [1]. It has been determined that vitamin D deficiency is common around the world for the last 20 years. It has been realized that this situation is a new risk factor for many chronic diseases such as increased skeleton disorders [osteoporosis], metabolic syndrome, cardiovascular diseases, some autoimmune diseases [multiple sclerosis, type 1 diabetes mellitus and inflammatory bowel disease] and cancer [colon, breast and prostate]. In subsequent studies it has been determined that vitamin D plays a functional role in the tissues that express vitamin D receptor. With the determination of the functional role of vitamin D in these tissues and organs, the variety of the diseases that vitamin D may play a role in has increased. Evidence shows that taking sufficient vitamin D is important to prevent skeletal and non-skeletal diseases [1–5]. In addition, it has been reported that when vitamin D is used in combination with radiotherapy (RT), it decreases the toxicity due to radiotherapy and increases the effect of radiotherapy [6].

Mechanism of action of vitamin D in cancer

The basic effect of vitamin D is on calcium and phosphorus metabolism and bone mineralization. At the same time, it provides immune tolerance and immunosuppressant

***Corresponding author: Yasemin Benderli Cihan,** MD, Kayseri Education and Research Hospital, Department of Radiation Oncology, Sanayi District, Ataturk Boulevard, Hastane Street, No. 78, 38010 Kocasinan, Kayseri, Turkey, Phone: +90 352 336 8884, Fax: +90 352 320 7313, e-mail: cihany@erciyes.edu.tr.
https://orcid.org/0000-0001-9295-4917

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by influencing many immune system cells. It changes dendritic cell differentiation and functions. It enhances T cell activity that is necessary for immunosuppressant by suppressing NFkb pathway necessary for T helper cell activation [4]. It is believed that it protects tissues from proinflammatory stress and cancer by these activities. It shows anti humoral effect by decreasing vitamin D proliferation, inhibiting angiogenesis, supporting cell differentiation and stimulating apoptosis [1, 3–5]. Vitamin D regulates several different proto-oncogen and tumor suppressor genes. These include p27/Kip1, c-myc, laminin, tenascin, fibronectin, cyclinC, c-fos, cjun, phospholipase C, ornithine, decarboxylase, and transforming growth factor [TGF]. It inhibits TGF-B epithelial cell proliferation in the growth factor target pathway [2, 5]. The antimitotic effect of vitamin D emerges by inhibiting G1/S from cell cycle phases. It shows this by up regulate cycline dependent kinase inhibitors p27 and p21 and by cycline D1. It reveals its effect of inhibiting tumor invasion and metastasis by inhibiting serine proteinase, metalloproteinase and angiogenesis [4, 5]. In the studies that have been conducted on the effects of vitamin D on health for about 20–30 years, evidence has been found that vitamin D deficiency increases cancer risk and mortality. In parallel with this, the number of the compile and meta-analysis studies that attempt to explain the possible evidence in the relationship between vitamin D and cancer more powerfully has been gradually increasing for the last 10 years. In the meta-analysis and compile studies, it has been revealed that high level of 25[OH]D has a protective effect on breast, colon and prostate cancers, and few studies has investigated whether or not it is protective against lung, pancreas and ovary cancers [1, 2].

The role of vitamin D in radiotherapy

In the studies it is emphasized that vitamin D status during diagnosis and treatment can affect cancer survival. In addition, the studies have started to reveal that using vitamin D together with radiotherapy has synergistic effect and it decreases the toxicities (radioprotector) depending on RT [6]. There has not been a randomized clinical trial and meta-analysis in the literature yet. Its inhibitor effect on the cell growth of 1,25[OH]2D3 in prostate, colon, gallbladder and breast cancers, malign cells and leukemia has been revealed by in vitro studies [1–7]. Polar et al. has revealed that vitamin D has an additive effect with radiotherapy in breast cancer cell culture. They have emphasized that vitamin D effect it by enhancing apoptosis, making cancer cell more radiosensitive by decreasing cell proliferation and stopping cell cycle [7]. Dunlap et al. has proved that radiotherapy and vitamin D has a synergistic action on human prostate cancer cells. Vitamin D stops cell cycle in G1/S and G2/M stage. Since cells are more radiosensitive in these stages, it is thought that giving vitamin D before radiotherapy will be an enhancer effect of sensitivity [8]. In addition to the radiosensitive effect of vitamin D, the radioprotector effect has been shown. Studies have shown that oxidative stress caused by radiation in the cell is modulated by modulating the mitogen-activated protein kinase (MAPK) signal and by the phospho-38 inactivation. In particular, it was emphasized that the inactivation of p38 MAPK pathway is very important for radioprotection [9]. Graham et al. have reported in their study that vitamin D decreases the liver damage due to radiotherapy [10]. Nasser et al. have emphasized that the topical administration of vitamin D ointment for patients with breast cancer is not superior to the standard ointment administrated in dermatitis due to radiation [11]. Ghorbanzadeh-Moghaddam et al. have investigated whether vitamin D deficiency cancer patients is related to the severity of acute proctitis due to radiation. It has been stated that vitamin D increases the severity of acute proctitis due to radiation. They have stated that the mechanisms under this relationship should be investigated and the efficiency of vitamin D treatment to prevent acute proctitis due to radiation should be evaluated [12]. In the study conducted by Akshay et al., vitamin D fortification was evaluated in 45 patients with terminal oral cancer exposed chemoradiation in terms of its effects on oral mucositis and swallowing performance. They stated that vitamin D fortification decreased toxicities related to therapy in terminal cancer considerably, by this way it decreased morbidity and enhanced the quality of life [13].

Conclusions

Although vitamin D is known as the bone hormone, it is also know that it has effects on autoimmune and allergic diseases, cardiovascular diseases, infection, obesity, aging process and the course of life because of its anti-inflammatory and immunomodulatory characteristics and its effects on cytokine levels. Its presence in the pathogenesis of several diseases has increased the importance of the determination of its deficiency and appropriate treatment. In vitro phase 1 and phase 2 studies showed that both radiosensitive and radioprotector effects were used in combination with radiotherapy and vitamin D. It shows its radiosensitive effect by increasing apoptosis

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in the cell and stopping the cell cycle in G1/S and G2/M stages. The radioprotector effect is modulated by modulating the MAPK and phospho-38 signaling pathways. It is seen that vitamin D use together with radiotherapy can have a positive effect on cancer treatment. It should be investigated whether toxicities due to radiation is prevented by vitamin D metabolites' increasing the induction of immunomodulator cells and the capacities of immune response cells. Use of 1,25[OH]2 Vitamin D3 analogs as an adjuvant immunomodulator for patients receiving radiotherapy should be evaluated. There is a need for studies to be done in this regard.

Conflict of interests: Authors have no conflict of interest.

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