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CASE REPORT

Potential Impact of Vitamin D in Pancreatic Ductal Adenocarcinoma

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ABSTRACT

A lethal disease, Pancreatic Ductal Adenocarcinoma (PDAC) is the third leading cause of cancer-associated deaths, with a 5-year survival rate of approximately 5% , secondary to unresectable or metastasis diseases, even in early stage. In the last decade, some progress in chemotherapy protocols for PDAC were performed to improve oncological management and to identify patients with less aggressive disease. Nevertheless, if current trends continue, PDAC is projected to become the second leading cause of cancer-related death by 2030.The shortage of vitamin D has garnered attention as an important factor in the progression of various types of cancer including PDAC. Recent reports revealed that vitamin D supplementation could inactivated surroundings of PDAC to a more quiescent, less tumor-supportive and could be a promising treatment option.

MINI REVIEW

Vitamin D is an interesting vitamin, which could play as a hormone with the active form of calcitriol, known as 1, 25-dihydroxycholecalciferol [1]. Calcitriol blood circulation produces effects via a nuclear receptor in multiple different locations, including tumor progression effect [2]. However, it is eventually not considered that vitamin D supplementation remarkably inhibits cancer occurrence [2,3]. Vitamin D supplementation has garnered attention as a promising treatment option in the progression of various types of cancer [4-8]. Those reports found that patients with PDAC had longer overall survival when they had sufficient prediagnostic plasma levels of 25 (OH) vitamin D, [8] indicating that vitamin D supplementation could be an effective treatment option inhibiting tumor progression [3].

PDAC is a lethal disease with a 5-year survival rate of approximately 5% because the majority of patients have unresectable tumors accompanying with distant metastasis, even in early stage [9]. The presence of dense stroma in cancer tissue is a prominent feature of PDAC. The stroma contains plenty activated-fibroblast, called 'cancer associated fibroblast (CAF)'. CAF plays an important role in metastatic spread [10]. However, CAF depletion accelerates PDAC and reduces survival in a murine model, unexpectedly [11]. This report importantly indicated that quiescent stromal cells inhibit PDAC cells, and, in contrast, activated stromal cells accelerate PDAC cells. Thus, there is a need for targeted therapy that inactivates CAFs. Recently, Ding et al. showed that the vitamin D receptor (VDR) exerts anti-fibrotic and anti-inflammatory effects by blocking TGF-β/SMAD signaling via genomic competition [12]. The same group also showed that transcriptional remodeling of pancreatic tumor stroma via VDR activation broadly weakened the capacity of human pancreatic-satellite cells (hPSCs) to support tumor growth [13]. As the VDR ligand pushes activated hPSCs toward a more quiescent phenotype, remodeled hPSCs re-establish a physiological and metabolic environment that deters tumor growth. These findings were not consistent with previous reports assuming that vitamin D supplementation did not decrease the risk of PDAC but improved the prognosis of patients with PDAC. Therefore, we postulated that vitamin D supplementation could be a promising targeted therapy for patients with PDAC.

To evaluate our hypothesis, we investigated the prognosis of patients with PDAC [14]. One hundred forty six patients with PDAC receiving chemotherapy or surgery were investigated for distant metastasis. Bone density change during treatment was evaluated by Computed Tomography (CT) number. The blood concentration of vitamin D before treatment was calculated by ELISA with available plasma, and they were 48 cases. We evaluated Distant Metastasis Free Survival time (DMFS) in all patients, and patients with decrease of bone density during treatment showed significantly shorter DMFS. Low vitamin D was a weak predictor of DMFS, but was not significant (p=0.08), maybe because of the sample size. We performed further analysis for bone density change and found that the chemotherapy impaired bone density in case of lower vitamin D concentration, and patients were not responder to chemotherapy. Therefore, the decrease of bone density would be a surrogate marker to predict distant metastasis. Moreover, it is possible that supplementary vitamin D would be a promising therapy to reduce the risk of metastatic spread.

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