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COMMENT

Vitamin D supplementation: a potential therapeutic agent for metastatic colorectal cancer

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Preclinical and epidemiological evidence suggests that vitamin D may have anti-cancer activities in patients with colorectal cancer. A recently completed, randomised Phase 2 trial of vitamin D_3 supplementation in patients with metastatic colorectal cancer has shown promising results, and a Phase 3 trial is currently underway.

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MAIN

Colorectal cancer (CRC) is the third most common cancer in both men and women in the United States.[1] It is also the second leading cause of cancer death in the United States,[1] as well as worldwide.[2] According to the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute, ~21% of CRC patients have metastatic disease with a 5-year survival rate of only 14%.[1] Therefore, novel treatment approaches that are safe, can delay progression, and prolong survival are urgently needed for this group of patients.

Vitamin D is an inexpensive, non-toxic, and easily accessible treatment that has demonstrated anti-neoplastic activities against CRC. Colon cancer cells express high levels of the vitamin D receptor (VDR).[3] In vitro studies found that by binding with VDR, vitamin D can induce apoptosis of colon cancer cells and counteract aberrant WNT-β catenin signalling.[4] In *APC*(min) mice, a model of intestinal tumorigenesis, tumour burden was increased by inactivation of the *VDR* gene and decreased by treatment with vitamin D or its synthetic analogue.[4]

To further explore these findings in CRC patients, observational studies were conducted to evaluate the association between plasma levels of 25-hydroxyvitamin D [25(OH)D] and patient outcome. Prospective cohort studies, with circulating 25(OH)D levels measured either prior to or at cancer diagnosis, consistently showed a high prevalence of vitamin D deficiency among CRC patients.[5] Moreover, CRC patients with higher 25(OH)D levels had longer survival times than those with lower levels.[5] In the initial report of 304 CRC patients from the Nurses' Health Study and the Health Professionals Follow-Up Study, subgroup analyses suggested a greater association of 25(OH)D levels with overall survival among patients with stage III or IV disease versus stage I or II.[6] However, in such studies that included patients with all stages of CRC, those with metastatic disease accounted for only a small fraction, resulting in inadequate power to evaluate the relationship between 25(OH)D levels and survival for this group of patients.

To date, two large prospective cohort studies have been conducted to specifically evaluate the association of circulating 25(OH)D levels with survival of patients with metastatic CRC.[7,8] One was conducted among 515 patients with stage IV CRC enrolled in the North Central Cancer Treatment Group 9741 trial, which found a significant association between higher 25(OH)D levels at diagnosis and improved overall survival among patients receiving FOLFOX (infusional fluorouracil, leucovorin, and oxaliplatin).[8] A later analysis of 1043 patients with metastatic CRC who were enrolled on Cancer and Leukemia Group B (Alliance)/SWOG 80405, a randomised Phase 3 trial of chemotherapy plus biologicals for first-line treatment,[9] confirmed the association between higher plasma 25(OH)D levels and improved progression-free and overall survival.[7]

Although observational studies support a positive association between 25(OH)D levels and survival of patients with metastatic CRC, they are not able to establish a causal role of higher 25(OH)D levels in improving survival. Vitamin D insufficiency can be a surrogate of worse health or a reflection of less favourable disease, which may confound the true relationship between vitamin D and survival. A double-blind Phase 2 randomised clinical trial, SUNSHINE, was therefore conducted to examine whether addition of high-dose vitamin D_3 (4000 IU/day), versus standard-dose vitamin D_3 (400 IU/day), to standard chemotherapy can improve outcomes in patients with metastatic CRC.[10] At study baseline, 91% of these patients had insufficient levels (<30 ng/ml) of 25(OH)D, with a median level of 16.1 ng/ml in the high-dose vitamin D_3 group and 18.7 ng/ml in the standard-dose vitamin D_3 group. During supplementation, median plasma 25(OH)D levels increased into the sufficient range (≥30 ng/ml) among patients receiving high-dose vitamin D_3 (median: 35.2 ng/ml), but remained unchanged with standard-dose vitamin D_3 (median: 18.5 ng/ml), supporting the ability of high-dose vitamin D_3 supplementation to raise 25(OH)D levels in patients with metastatic CRC undergoing chemotherapy. Moreover, patients receiving high-dose vitamin D_3 had improved progression-free survival compared with those receiving standard-dose vitamin D_3 (median progression-free survival: 13.0 months versus 11.0 months; stratified log-rank $P = 0.03$), Importantly, high-dose vitamin D_3 supplementation did not result in any added toxicity.

To determine whether vitamin D supplementation should be considered a part of standard treatment of metastatic CRC, a confirmatory multicentre, double-blind, randomised Phase 3 trial of vitamin D_3 supplementation in combination with standard chemotherapy among previously untreated patients with

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metastatic CRC called SOLARIS is currently underway through the Alliance for Clinical Trials in Oncology (ClinicalTrials.gov identifier: NCT04094688). The trial will enrol 400 patients with a greater diversity in race and geographical residence, as well as adequate power to detect a progression-free and overall survival benefit.

The evolution and development of vitamin D into a potential therapeutic agent for cancer is a prime example of the importance of research on diet and lifestyle factors and the critical role that they may play in cancer pathogenesis and treatment. Repurposing a safe, affordable, and accessible agent such as vitamin D could potentially have a large and wide-reaching impact globally, even in regions with fewer resources. Robust funding and support are therefore needed to conduct further studies on the biological mechanisms underlying the activity of vitamin D and other modifiable factors in CRC, such that their acceptance and incorporation into standard paradigms of patient care and management may be facilitated.

AUTHOR CONTRIBUTIONS

C.Y. and K.N. both contributed to the writing, revision, and approval of this manuscript.

ADDITIONAL INFORMATION

Ethics approval and consent to participate Not applicable.

Data availability Not applicable.

Competing interests K.N. declares research funding from Evergrande Group, Genentech, Gilead Sciences, Pharmavite, Revolution Medicines, Tarrex Biopharma, and Trovagene; advisory board participation for Array Biopharma, Bayer, Eli Lilly and Company, Genentech, and Seattle Genetics; and consulting for Tarrex Biopharma. C.Y. declares no conflicts of interest.

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