

Approaches to Optimizing Vitamin D Therapy in Prostate Cancer

A preventive role for vitamin D in the natural history of prostate cancer was suggested in 1992 with the finding that United States mortality rates from prostate cancer were inversely correlated with the availability of sunlight, the major source of vitamin D.¹ Subsequent laboratory research demonstrated that prostate cancer cells possess receptors for the hormonal form of vitamin D (1,25-dihydroxyvitamin D, aka calcitriol) and confirmed that 1,25-dihydroxyvitamin D exerts antiproliferative effects on these cells. The realization that 1,25-dihydroxyvitamin D serves as a “brake pedal” on prostate cancer cells suggested that this brake could be applied therapeutically, particularly after androgen withdrawal ceased to inhibit cell proliferation.

In the following decade pleiotropic anticancer effects of 1,25-dihydroxyvitamin D on prostate cells were demonstrated by numerous preclinical studies.² Several phase II trials in prostate cancer showed evidence of additive or synergistic effects when calcitriol was added to standard chemotherapies.³ Thus, in November 2007 the news of a significantly shorter survival in the treatment arm of a large phase III trial that used a high dose of 1,25-dihydroxyvitamin D (the ASCENT-2 trial in men with castration resistant prostate cancer) was a disappointment, and cast a temporary pall over calcitriol based therapies.⁴

The results of ASCENT-2 were not an indictment of a calcitriol based strategy in general. Rather they indicated that there were flaws in the specific regimen of 1,25-dihydroxyvitamin D administration or in the design of the trial.^{4,5} The principal toxicity of calcitriol is its effect on increasing serum calcium levels. Because serum levels of ionized calcium influence numerous physiologic processes, including cell growth as well as neural and cardiac conduction, the engineering challenge is to increase 1,25-dihydroxyvitamin D levels high enough to inhibit prostate cancer cells without perturbing vital physiologic processes. There are several approaches to this challenge. One is to use modified forms of 1,25-dihydroxyvitamin D (vitamin D analogs), eg paricalcitol and doxercalciferol, that have reduced

calcemic effects.^{6,7} Another approach is to use 1,25-dihydroxyvitamin D in a modified, less calcemic form of drug delivery (as in ASCENT-2). A third approach uses 1,25-dihydroxyvitamin D or analogs in combination chemotherapy. Yet another approach is to use treatments that sensitize prostate cells to 1,25-dihydroxyvitamin D and, thus, potentiate the effects of 1,25-dihydroxyvitamin D locally. It is in this context that the recent results of Koike et al in this issue of *The Journal* (page 000) are of interest.

The authors demonstrate a role for survivin, a member of the inhibitors of apoptosis family, in the antiproliferative effects of 1,25-dihydroxyvitamin D. Survivin over expression has been reported previously in association with increased resistance to chemotherapy in prostate cancer cells. Koike et al used small interfering RNA (siRNA) to knock down survivin, and showed that anti-survivin siRNA inhibited cell proliferation and tumor growth in LNCaP and PC-3 prostate cancer cells. 1,25-Dihydroxyvitamin D decreased survivin gene expression and cell proliferation in LNCaP and PC-3 cells. Notably DU145 cells, whose proliferation was not suppressed by 1,25-dihydroxyvitamin D alone, showed significant inhibition of proliferation by 1,25-dihydroxyvitamin D after the transfection of anti-survivin siRNA. Thus, knocking down survivin expression may be a future therapeutic option in calcitriol based therapies.

As the authors note there are obstacles to the translation of these findings to the clinic, including an efficient delivery system for siRNA. Moreover the doses of 1,25-dihydroxyvitamin D required to inhibit cell and tumor growth in these studies are higher than is achievable in men without inducing hypercalcemia. The calcemic effects of 1,25-dihydroxyvitamin D may be more important than previously recognized in light of evidence from prospective studies that high normocalcemia (serum calcium levels that are high but within the normal range) is associated with an increased risk of death from prostate cancer.⁸ These considerations notwithstanding, the findings of Koike et al offer encouraging evidence that a sensitization approach to calcitriol

based therapies for prostate cancer may be feasible. It will be valuable to repeat the *in vivo* experiments using vitamin D analogs and in the setting of a calcium restricted diet.

The recognition that vitamin D inhibits prostate cancer cell proliferation and prostate cancer metastasis to bone⁹ offers tantalizing glimpses into new therapeutic vistas.¹⁰ Translating the vitamin D sen-

sitivity of prostate cancer cells into effective therapies is a worthy goal, and the report by Koike et al represents one of several creative steps toward achieving it.

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