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The role of vitamin D in oncology: where are we?

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INTRODUCTION

Preclinical studies, using in vitro and in vivo models, show that vitamin D (vitD) is capable of inhibiting neoplastic transformation and progression by inducing cell differentiation, inhibiting proliferation of the neoplastic clone, and performing multiple other biological activities of an anti-inflammatory, immunomodulatory, pro-apoptotic and anti-angiogenic nature.
From a clinical point of view, circulating levels of vitD and its active metabolites have been linked to improved survival of cancer patients. Multiple randomised trials have been conducted, albeit with conflicting results, on the possible impact of vitD supplementation on human cancer incidence, mortality and survival.
This short review of the literature is intended to take stock of the latest preclinical and clinical data and the possible role of vitD in oncology.

BIOLOGICAL MECHANISMS OF ACTION

VitD, produced by the conversion of 7-dehydrocholesterol by UV radiation in the skin, is the precursor of the potent multifunctional hormone calcitriol [1,25-dihydroxy-vitamin D_3 (1,25$(OH)_2D_3$)], which is produced by dihydroxylation in the liver and kidney by cytochrome P450 [1-4]. Through binding to its receptor (VDR), calcitriol regulates, directly or indirectly, 3-5% of the human genome.
An initial level of interaction between vitD and neoplastic transformation and progression relates to the local biosynthetic capacity of the enzyme CYP27B1, whose expression is reduced in some tumours in a stage- and differentiation-dependent manner. In this context, variations in VDR expression at the intra-tumour level may also influence the biological aggressiveness of the neoplasm by modulating the autocrine, paracrine and intracrine action of vitD [1-4].
VitD's potential anti-cancer action is expressed through predominantly genomic mechanisms, but also through non-genomic mechanisms involving, for example, the VDR and endoplasmic reticulum stress protein 57 (ERP57) [5].
The genomic actions of vitD involve the modulation of a wide range of mediators, which regulate pathways of proliferation, apoptosis, and differentiation of tumour cells. For instance, in the three malignancies with the most evidence, including clinical findings, of potential sensitivity to the anti-neoplastic effects of vitD/VDR (breast, prostate and colorectal cancer), this action is expressed through the modulation of proliferative pathways regulated by oestrogen, androgen and the WNT/β-catenin system, both in partially differentiated tumour cell populations and in neoplastic stem cell populations (CSCs), respectively. In addition, signalling through the vitD/VDR axis may also influence the interaction between cancer cells and the tumour microenvironment (TME) in an anti-tumour direction, through modulation of invasive and metastatic capacity and the inhibition of pro-inflammatory and pro-angiogenic pathways [1-4]. Molecular mechanisms involved in the regulation of the anti-tumour activities of vitD include a bi-directional role of a large panel of micro-RNAs (miRNAs), which on the one hand are regulated by the vitD/VDR system, mediating its downstream anti-tumour effects, and on the other hand can regulate the expression of VDR and CYP24A1, modulating the sensitivity of tumour cells to the action of vitD [1-4].
In most, although not all, studies using animal models, dietary vitD supplementation and/or administration of calcitriol and its analogues delay transformation and inhibit neoplastic progression. These models include those of pre-neoplastic lesion progression, human tumour xenografts, models of spontaneous or diet-induced carcinogenesis, models of chemical or known carcinogen-induced carcinogenesis and transgenic models of tumour development [1-4].

CLINICAL FINDINGS

Although the findings from epidemiological studies and randomised clinical trials have not conclusively documented clinically relevant

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effects of vitD levels on the most significant cancer outcomes, overall, the data available to date indicate a greater effect on cancer mortality than on cancer incidence. This suggests possible biological effects on progression or promotion mechanisms rather than on those linked to neoplastic transformation or initiation. These findings (summarised briefly below) would place interventions based on dietary supplementation or pharmacological administration of vitD, calcitriol and related molecules within the conceptual framework of chemoprevention.

Impact on cancer incidence

In three recent systematic reviews of the literature with meta-analysis of pooled data [6-8] (Table I) the relative risk (RR) of developing malignant neoplastic disease in the vitD-supplemented group ranged from 0.98 to 1.03, without significant heterogeneity. These figures, along with the results of the three largest single studies (RECORD, ViDA and VITAL) [9-11], do not support a significant association between vitD supplementation and cancer incidence. In general, in the studies analysed, there is no evidence of a differential effect in particular subgroups.

Impact on cancer mortality

Although the reductions in cancer mortality have not always reached statistical significance in individual studies, in three of the four main studies [9,11,12], there was surprising uniformity in the estimated reduction in the risk of death from cancer, ranging from 14 to 18%, with the exception of the ViDA study [10], where the reduction was minimal (7%). Consequently, the four available meta-analyses [6-8,13] have documented a RR of cancer mortality ranging from 0.85 to 0.88 in favour of the vitD supplementation-based intervention, without significant heterogeneity, reaching statistical significance in three meta-analysis studies (see Table I) [6,7,13].

Some subgroup analyses have indicated a greater likelihood of benefit in terms of mortality reduction, for studies that included subjects of both sexes and with no previous history of cancer, for studies that used daily vitD administration, and for studies with relatively low doses of vitD and that achieved circulating 25(OH)D levels < 100 nmol/L [6-8]. An additional subgroup analysis has suggested that the reduction in cancer mortality is restricted to interventions using $vitD_3$, but is not evident for interventions using $vitD_2$ [13].

INTERPRETATION OF AVAILABLE DATA AND LINES OF FUTURE DEVELOPMENT

The clinical findings cited above suggest, as already mentioned, a prevailing effect of vitD on progression or promotion mechanisms rather than on those linked to neoplastic transformation or initiation. This is also supported by the results of a sub-analysis of the VITAL study, which indicate a significant reduction in the incidence of advanced cancers (metastatic or fatal, hazard ratio - HR -0.83, 95% CI 0.69-0.99, P = 0.04) in the vitD-treated group, particularly in the subgroup of subjects with normal body mass index (P for interaction = 0.03) [14]. Aligned with these results, the first randomised trial, conducted in patients with advanced colorectal neoplasia undergoing chemotherapy, found a trend in favour of high doses of $vitD_3$ over standard doses, with an advantage of approximately 2 months in median progression-free survival (PFS; 13 vs 11 months, log-rank P = 0.07) and an HR in multivariate analysis of 0.64 (1-sided 95% CI, 0-0.90; P = 0.02) [15].

Finally, the far from negligible impact of vitD supplementation in the context of prevention of skeletal complications and palliation of symptoms in advanced stages of disease should also be mentioned [16,17].

Despite the interest and considerable number of both preclinical and clinical studies reported to date, important gaps remain in the knowledge regarding the potential effect of vitD in reducing tumour progression and cancer mortality [18].

From a preclinical point of view, recent literature has revealed an important role of vitD in reversing multidrug resistance, through interference with epithelial mesenchymal transition mechanisms (EMT), which support drug resistance and favour metastatic spread, and through modulation of specific miRNAs linked to neoplastic progression, thus suggesting its use in the context of advanced disease and in combination with other therapeutic strategies. From a clinical point of view, however, further studies are

TABLE 1.
Main meta-analyses conducted on the impact of vitD on cancer incidence and mortality in recent years

Incidence

Author	No. Trials	No. Patients	Cases (VitD)	Cases (cont)	RR	95% IC	P	Heterogeneity	Ref.
Zhang et al.	10	81.362	3716 (9,16%)	3799 (9,26%)	0,99	0,94-1,03	0,532	No	6
Keum et al.	10	-	6.537		0,98	0,93-1,03	0,420	No	7
Goulão et al.	24	18.440	540 (5,66%)	521 (5,85%)	1,03	0,91-1,15	n.s.	No	8

Mortality

Author	N. trial	No. Patients	Cases (VitD)	Cases (cont)	RR	95% IC	P	Heterogeneity	Ref.
Zhang et al.	7	77.653	821 (2,11%)	942 (2,43%)	0,87	0,79-0,95	0,003	No	6
Keum et al.	5	-	1,591		0,87	0,79-0,96	0,005	No	7
Goulão et al.	7	11.202	150 (2,67%)	170 (3,04%)	0,88	0,70-1,09	n.s.	No	8
Zhang et al.	5	39.197	397 (2,02%)	468 (2,39%)	0,85	0,74-0,97	0,01	No	13

needed not only to confirm the effect of reducing cancer mortality, but above all to clarify the potential role of vitD in tumours of specific anatomical districts, the possible interactions with specific tumour driver genetic alterations, the possible modulation of protective effects in specific individual genetic contexts (e.g. VDR polymorphisms) [18], in order to relate the therapeutic or preventive use of vitD to a context of precision Oncological treatment.

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