blood advances

Vitamin D insufficiency in CLL: a modifiable prognostic factor?

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Comment on Tadmor et al, page 3840

In this issue of *Blood Advances,* Tadmor et al[1] used the Macccabi Healthcare Services Database of ~2.5 million insured patients in Israel to evaluate the association between vitamin D supplements (or their analogs) with time to first treatment (TTFT) and treatment-free survival ([TFS]; need for chronic lymphocytic leukemia [CLL] treatment or death due to any cause) during active surveillance in patients with newly diagnosed CLL.

Vitamin D is a critical nutrient that plays an essential role in skeletal homeostasis and maintenance of serum calcium levels. Vitamin D also has a number of important cellular effects, including regulation of proliferation, differentiation, apoptosis, and angiogenesis.[2] Vitamin D insufficiency is present in ~1 billion individuals worldwide[3] and is associated with elevated risk of multiple cancers, including colorectal cancer, breast cancer, and lymphoid malignancies.[4] Notably, vitamin D insufficiency has been associated not only with the risk of cancer diagnosis but also worse prognosis in numerous solid tumors as well as lymphoid malignancies.[4] Indeed, a recent systematic review identified a significant association between vitamin D levels and patient outcomes in several lymphoid malignancies with a pooled risk of disease progression of 1.93 among those with vitamin D insufficiency.[5] Both normal and neoplastic hematopoietic cells express the vitamin D receptor, and gene expression profiling as well as protein analysis have demonstrated the vitamin D receptor is highly expressed in CLL cells relative to normal B cells.[6] Studies have also demonstrated that pharmacologic doses of vitamin D analogs cause preferential apoptosis of CLL B cells in vitro through mechanisms independent of p53, via the mitochondrial pathway (caspase 3 and 9 dependent).[6]

In 2011, our group at Mayo Clinic evaluated the association between vitamin D insufficiency and prognosis in a discovery cohort of 390 patients with CLL (vitamin D assessed within 12 months of diagnosis), as well as a separate validation cohort of 153 patients with untreated CLL participating in a prospective observational study.[7] Approximately 90% of individuals in both cohorts had Rai stage 0 or I disease. Vitamin D insufficiency was strongly associated with a shorter TTFT (hazard ratio [HR], 1.66; $P = .005$), with a nearly identical HR for shorter TTFT in the validation cohort. On pooled analysis across cohorts, vitamin D insufficiency was associated with shorter TTFT after adjusting for age, sex, Rai stage, and cytogenetic analysis by interphase fluorescence in situ hybridization (FISH), as well as CD38, ZAP-70, CD49d, and immunoglobulin heavy chain gene (*IGHV*) status (HR, 1.47; $P = .008$). The association of vitamin D insufficiency with shorter TTFT was subsequently confirmed in an Italian cohort of 130 patients with Binet stage A.[8] Although this evidence across 3 independent cohorts of patients with CLL is compelling, it is certainly possible that vitamin D insufficiency is simply a marker associated with more rapid CLL progression rather than mechanistically contributing to it.

Against this backdrop, Tadmor et al conducted a well-designed retrospective study evaluating the impact of vitamin D supplementation in patients with early stage CLL identified in the Maccabi Healthcare Services Database. Among 3474 patients with CLL seen between January 2000 and December 2022, a total of 931 patients (27%) received vitamin D supplementation (or a vitamin D analog) for at least 6 months during the active surveillance phase of CLL management (median exposure, 28 months). The median TFS among users of vitamin D supplements was 169 months, compared with 84 months among those who did not use vitamin D supplements, using an inverse probability of treatment weighting approach. The authors subsequently conducted multivariate analyses taking into account age, sex, Binet stage, complete blood count, lactate dehydrogenase, and absolute lymphocyte count, and found that supplementation with vitamin D was associated with longer TFS (HR, 0.91; 95% confidence interval, 0.85-0.97; $P = .004$).

The authors conducted several subanalyses to evaluate the robustness of these findings. First, they used a quasi-control design to assess whether use of another vitamin (vitamin C supplementation) was also associated with shorter TTFT to evaluate the specificity of these findings and determine whether supplement use is simply a marker of health behaviors/lifestyle. Vitamin C supplementation was not associated with a longer TTFT or TFS, suggesting that the observed findings were specific to the effects of vitamin D supplementation (and not simply "healthy user" bias). The authors also evaluated the use of alfacalcidol (a vitamin D analog) in a subset of patients (n = 537) who reported taking this supplement for the treatment of osteoporosis and found that the consumption of alfacalcidol was associated with longer TFS in this subset.

Despite its many virtues, the study also has limitations. When evaluating the impact of vitamins and minerals on clinical outcomes, it is critical to distinguish between both disease prevention (ie, chemoprevention) and therapeutic effect (after the disease is present) as well as the distinction between replacement of a deficiency and supplementation. Although the Tadmor study would clearly fall in the therapeutic category, vitamin D levels were not available for all treated patients, and hence it is unknown what proportion of those taking vitamin D would fall in to the replacement vs supplementation categories. In addition, information about novel prognostic biomarkers (eg, *IGHV* mutation status and cytogenetic abnormalities evaluated by FISH) were also not available for the entire cohort; making it difficult to discern how these factors may have contributed to the differences in TTFT and TFS between groups.

Nonetheless, the findings of Tadmor et al have potentially important implications for the 80% to 90% of newly diagnosed patients with CLL who have asymptomatic early stage disease, of whom 30% to 50% have suboptimal vitamin D levels.[7] Although adequately powered randomized phase 3 clinical trials would provide the definitive evidence on the benefit of providing vitamin D supplementation for patients with early stage CLL, withholding replacement therapy among individuals with vitamin D deficiency is challenging because it deviates from standard medical practice.[9] We opened a randomized phase 2 clinical trial using vitamin D supplementation in patients with non-Hodgkin lymphoma (including CLL) at Mayo Clinic in 2013 (NCT01787409). Although this trial compares the effect of immediate vs delayed replacement of vitamin D (ie, all patients get replacement therapy) on proxy measures of disease progression (eg, changes in absolute lymphocyte count), accrual has been slow due to the reluctance of both patients and treating hematologists to delay replacement in deficient patients. It should be noted that in clinical trials for other medical conditions in which the presence of vitamin D deficiency at diagnosis has been associated with worse outcomes (such as multiple sclerosis), replacement therapy has not yielded a meaningful improvement in outcomes.[10]

In conclusion, the findings of Tadmor et al provide suggestive evidence that, beyond vitamin D insufficiency being associated with shorter TTFT in patients with asymptomatic newly diagnosed CLL, vitamin D replacement may have the potential to (at least partially) abrogate that risk. Given the expression of the vitamin D receptor on CLL cells and preferential killing of CLL B cells exposed to vitamin D analogous in vitro,[6] this possibility is biologically plausible and raises the prospect that vitamin D insufficiency is a modifiable prognostic marker in patients with early stage CLL. Given the generally low toxicity of vitamin D replacement, the report of Tadmor et al should stimulate additional studies to more rigorously evaluate this possibility.

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