thoughts on its possible etiology. A reactive process associated with a predominant NK-cell response across the gastrointestinal tract seems to be ongoing in these patients, as evidenced by the long persistence of the lesions on follow-up. It would be interesting to study the level of expression of cytokines such as IL-15 and IL-1, which are abundant in the mucosa-associated lymphoid tissue (MALT), especially in patients with celiac disease and other inflammatory bowel disorders, and have been shown to stimulate growth of immature NK cells found in MALT.

As a final commentary, considering that the single most common anatomical site of involvement in Mansoor’s cases is the colon, one might consider the diagnostic term “NK-cell colitis” (atypical or not) as possibly more fitting than “enteropathy.” In that regard, despite the lack of symptoms and a presumption of normal immunity, one wonders whether stains for cytomegalovirus or other human herpesviruses should have been performed in these lesions, to exclude infections known to be recognized by NK cells. And, was there a family history of autoimmune diseases, immunodeficiency, or hematologic malignancies? Future reports of this fascinating new disease entity may have to address these issues. Nonetheless, we commend the authors for what George Orwell famously observed: “To see what is in front of one’s nose needs a constant struggle.”

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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Comment on Shanafelt et al, page 1492

CLL: a supplementary question?

Chris Pepper and Chris Fegan  CARDIFF UNIVERSITY

In this issue of Blood, Shanafelt and colleagues provide the first evidence that vitamin D deficiency is a risk factor for disease progression in chronic lymphocytic leukemia (CLL). Their findings imply that dietary vitamin D supplementation could potentially modify the natural history of this incurable disease.

It has been estimated that approximately 1 billion people worldwide have vitamin D insufficiency due to reduced exposure to sunlight or inadequate dietary intake. Vitamin D plays a central role in maintaining serum calcium and skeletal homeostasis but is also involved in the regulation of other vital cellular processes including differentiation, proliferation, apoptosis, and angiogenesis. Although its precise mechanisms of action remain incompletely resolved, vitamin D predominantly exerts its effects through the binding of calcitriol, the active form of vitamin D, to its cognate nuclear vitamin D receptor (VDR). A heterodimer, formed with the retinoid X receptor (RXR), then acts as a transcription factor by binding to specific genomic sequences (vitamin D response elements) resulting in altered gene transcription. The classic target organs of vitamin D are the intestines, kidney, and bone, but several other tissues also express VDRs including normal and neoplastic hematopoietic cells.

A large number of studies have investigated a possible role for vitamin D in cancer prevention but, until now, none have shown that this secosteroid hormone is important in CLL. The study of Shanafelt et al clearly demonstrates that vitamin D insufficiency is an independent risk factor in this disease. Remarkably, its prognostic power was evident even in early-stage patients (Rai stage 0) and retained independent prognostic significance in the presence of most of the major known risk factors in multivariate analysis. From a clinical perspective, vitamin D insufficiency represents the first potentially modifiable prognostic marker in CLL by presenting the opportunity for patients to have their serum vitamin D levels checked and, if they are deficient, vitamin D supplements administered to correct the deficit. Given that appropriate vitamin D supplements are likely to have a minimal side-effect profile, it seems plausible that they could be safely incorporated into the “watch-and-wait” strategy currently used for early-stage disease patients. If nothing else, this may well have positive psychological effects for many patients who struggle with feelings of powerlessness after being told they have leukemia that may progress.

Although we still await formal proof that normalizing vitamin D levels can improve clinical outcomes in this disease, there are certainly grounds for optimism. Previous gene expression profiling and protein analysis identified that the VDR is highly expressed in CLL cells compared with normal B and T lymphocytes. Furthermore, pharmacologic doses of a vitamin D analog caused preferential in vitro cell killing in primary CLL cells through a p53-independent mechanism. Taken together, the evidence points toward a potentially important role for vitamin D not only as a prognostic marker but also as a therapeutic target in CLL. On a cautionary note, it would appear that vitamin D levels are subject to heritable genetic variation with 3 pivotal polymorphisms recently being identified.

Furthermore, VDR polymorphisms have been associated with the risk of developing cancer and cancer progression although there are no reported studies in CLL. Therefore, it may not be possible to correct vitamin D insufficiency with dietary supplementation in at least some CLL patients. Only a prospective, well-designed, randomized, control clinical trial of vitamin D supplementation will prove whether we have truly “crossed the Rubicon” in CLL and identified a way of modifying the clinical course of this incurable disease with a simple vitamin tablet.
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Comment on Hsu et al, page 1605

How “immunomodulatory” are IMIDs?

Constantine S. Mitsiades  DANA-FARBER CANCER INSTITUTE

In this issue of Blood, Hsu and colleagues report that the immunostimulatory effect of lenalidomide on natural killer (NK)–cell function is profoundly suppressed by concurrent dexamethasone (Dex) therapy in multiple myeloma (MM) patients.1 These results could have major implications for the design of clinical trials combining lenalidomide and immunotherapies with the intent to stimulate the anti-MM activity of the latter.

Lenalidomide and pomalidomide are thalidomide derivatives and, along with their parent compound, are frequently referred to as immunomodulatory derivatives (IMIDs) because of their shared ability to modulate immune responses, including stimulation of NK-cell and T-cell activity against multiple myeloma (MM) cells in preclinical models.2 Thalidomide and lenalidomide are approved by the Food and Drug Administration (FDA; in combination with Dex) for the treatment of MM, while clinical trials of pomalidomide (CC-4047) already show activity even in lenalidomide- and bortezomib-refractory MM.3 Other proposed mechanisms of IMID action against MM (reviewed by Anderson)4 include direct activation of proapoptotic cascades in MM cells, perturbation of MM-stroma interactions, and antiangiogenic effects. However, the relative contribution of these mechanisms to the clinical anti-MM activity of the IMID class has not been formally addressed.

Hsu et al show that peripheral blood mononuclear cells (PBMCs) from lenalidomide–Dex–treated MM patients who were responding to their treatment exhibit, compared with baseline samples, decreased activity of NK cells against target tumor cells in vitro. Similar results were obtained with healthy donor NK cells treated in vitro with lenalidomide–Dex versus lenalidomide only. Mechanistically, Dex abrogated the lenalidomide–induced stimulation of CD4+ T-cell proliferation and interleukin–2 (IL–2) production and down-regulated the activating receptors NKG2D and Nkp46 on NK cells. The suppressive effects after in vitro or in vivo Dex exposure were not rapidly reversible, but persisted even after several days of in vitro culture with high (including both clinically achievable and supra-pharmacologic) concentrations of lenalidomide and in the absence of Dex. The adverse impact on NK-cell activity was observed with Dex concentrations as low as 0.1 μM. These observations are qualitatively consistent with the known pleiotropic immunosuppressive effects of Dex, including recent in vitro data by Gandhi et al that Dex inhibits lenalidomide–induced IL–2 production by stimulated T cells and secretion of interferon–γ and Granzyme B by NK cells from healthy donor PBMCs.5

The main message of the article by Hsu et al is not that lenalidomide is completely devoid of “immunomodulatory” activity in MM patients, but that with Dex administration, this immunostimulatory effect is severely compromised, if present at all. This suggests that other mechanisms are primarily responsible for the observed clinical responses with lenalidomide–Dex. Interestingly, MM patients receiving lenalidomide (without Dex) as maintenance therapy after autologous stem cell transplantation have longer time to progression than patients receiving placebo.6,7 If this clinical outcome is confirmed to be related, even in part, to the lenalidomide–enhanced immunologic effect on residual MM tumor cells, the absence of concurrent Dex use in the maintenance setting would further support the observations by Hsu et al and Gandhi et al.

A key emerging question is how the design of future clinical trials of lenalidomide–containing combination regimens should include Dex. Until more data become available, it is important to consider the specific goals for lenalidomide in each specific regimen. If the goal is to maximize direct anti-MM-cell cytotoxicity, inclusion of Dex with lenalidomide is compatible with the FDA approval of lenalidomide in combination with Dex and capitalizes on the demonstrated clinical potency of this doublet, without running counter to the data of Hsu et al. However, if adding lenalidomide to an investigational regimen seeks to augment immunologic responses of, for example, a monoclonal antibody which stimulates MM-cell killing by immune effector cells (rather than inhibition of surface receptors which trigger cell survival), Dex use should be viewed with caution. It may even be worth considering a Dex–sparring approach, unless specific data are available to inform a design through which the suppressive effect of Dex can be bypassed in the clinical context of the trial. Even for combinations without a designated immunotherapeutic component, the question of Dex dose remains pertinent, given the safety and efficacy of single-agent lenalidomide; the superior safety (including lower...
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