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Toward optimizing pomalidomide therapy in MM patients

Klaus Podar UNIVERSITY OF HEIDELBERG

In this issue of Blood, Sehgal et al report on the clinical and pharmacodynamic analysis of pomalidomide dosing strategies in multiple myeloma (MM) and their impact on immune activation and cereblon targets. The particular novelty of this study lies in the direct correlation of immune effects triggered by pomalidomide with clinical responses in MM patients. Results of this study will stimulate many additional studies.

Because of remarkable responses, the second-generation immunomodulatory drug (IMiD) pomalidomide (Pomalyst; Celgene) has been granted accelerated US Food and Drug Administration and European Medicines Agency approval in February 2013 and in August 2013, respectively, for the treatment of adult patients with relapsed/refractory MM who have received ≥2 prior treatment regimens, including lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy. Functionally, preclinical data have shown that pomalidomide mediates direct anti-MM cell activity as well as immunomodulatory and antistroma support activities. Data on pomalidomide-mediated immune activation in vivo are limited. The optimal dosing schedules of both pomalidomide and concurrent steroids need to be clarified.

Sehgal et al randomized 39 patients with relapsed MM refractory to lenalidomide and bortezomib into 2 treatment cohorts using either continuous (2 mg for 28 of 28 days) or intermittent (4 mg for 21 of 28 days) pomalidomide dosing schedules. Using extensive analyses, the authors demonstrate that pomalidomide induces rapid changes in immune profile and function. Specifically, they show pomalidomide-induced increases of both T and natural killer (NK) cells and their activation in the peripheral blood as well as in the bone marrow. Objective treatment responses correlated with pomalidomide-induced increases in interferon-γ and tumor necrosis factor-α–producing CD8+ and multifunctional T cells but not NK cells. Moreover, gene expression profiling analysis showed that genes altered by pomalidomide treatment in CD138–negative cells predominantly belong to immune pathways, ie, in lymphocytes. These data highlight the eminent role of immunomodulation as part of the pomalidomide-induced in vivo anti-MM activity. They also indicate that the biology of innate lymphocytes in the context of pomalidomide treatment requires further investigation. Comparable responses were observed under both dosing schedules, with significantly greater incidence of grade 3/4 side effects in the intermittent dosing schedule. These results suggest that the lower dosing schedule of pomalidomide may be sufficient in the clinical setting. However, future studies need to explore whether treatment holidays as part of intermittent dosing schedules restore sensitivity to pomalidomide. Importantly, baseline levels of CD4/CD8+ T cells did not predict response rates to pomalidomide treatment. Therefore, a high need remains for those biomarkers that determine which patients are likely to benefit from pomalidomide-containing immunotherapies. Moreover, previous data demonstrate that dexamethasone synergizes with pomalidomide in terms of tumor regression. Based on the present data, dexamethasone also blunts pomalidomide–mediated T-cell activation. Optimization of pomalidomide/dexamethasone combination therapy using intermittent or modified low-dose dexamethasone is therefore required.

Another important finding of this study is that pomalidomide treatment increases the expression of immune checkpoint modulators B– and T-lymphocyte attenuator (BTLA) on T cells and T–cell immunoglobulin and mucin-domain containing-3 (Tim-3) on NK cells in MM. These data indicate a potential therapeutic role for combining pomalidomide with next-generation immune checkpoint inhibitors directed against Tim-3 and BTLA in MM. Importantly, pomalidomide induced changes of Tim-3 and BTLA expression, but not PD-1, currently the best investigated immune checkpoint protein in T cells. In contrast to normal plasma cells, PD-1 ligand is expressed on primary MM cells and induced by cytokines and bone marrow stromal cells, highlighting the intimate functional interrelation of the nonimmune and immune compartments within the MM bone marrow microenvironment. The efficacy of inhibiting the PD-1/PD-L1 pathway has been demonstrated in several preclinical studies of MM. A clinical study that evaluates the activity of pomalidomide in combination with the anti–PD-1 inhibitor...
Transcriptional regulators such as Ebf1 have been shown to support B-cell differentiation by coordinating the expression of downstream transcription and signaling factors with the activation of the immunoglobulin gene recombination machinery. They also preserve B-lineage fidelity by suppressing expression of signaling and transcription factors that promote alternate fates latent in these early precursors. The outcome of this complex transcriptional process is the generation of the humoral arm of the immune system through the production of a diverse repertoire of properly selected mature B cells capable of antibody production on antigenic challenge. Loss-of-function mutations in EBF1 and other B-lineage transcriptional regulators, such as PAX5, are associated with B-ALL in humans. Notably, the leukemogenic effect of these mutations manifests at the heterozygous level with differentiation only partly affected, suggesting that other dose-dependent functions of these factors in B-cell precursors are contributing to the disease state.

It might seem surprising that impaired function of EBF1 would lead to B-ALL, because genetic studies in mice have shown that Ebf1 supports proliferation of B-cell precursors and mature B cells. Prasad et al identify a significant reduction in homologous recombination (HR) DNA repair genes in the
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