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REFERENCES

LYMPHOID NEOPLASIA

Comment on Hsu et al, page 1605

How “immunomodulatory” are IMIDs?

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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 Anderson4) 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, 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-sparing 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
infection rates) of lenalidomide-Dex treatment with lower versus higher Dex dose⁹, and the high rates and durability of responses to lenalidomide-bortezomib in a study where most patients did not receive Dex.¹⁰

This study by Hsu et al triggers captivating new questions. What is the impact of Dex on patients’ NK-cell activity against autologous MM cells and does it correlate with clinical outcome after lenalidomide-Dex treatment? Does the impact of Dex on lenalidomide-induced immunostimulation depend on disease stage, underlying degree of MM-associated immunoparesis, status of prior treatment(s), or concomitant use of other therapeutics (eg, proteasome inhibitors)? Will this study’s results differ quantitatively or qualitatively in MM patients who are younger or without renal impairment (ie, in patient populations different from those of the current study) or with thalidomide or pomalidomide treatment? Do the in vivo interactions of the tumor cells with their microenvironment alter the balance between the opposing immunologic effects of lenalidomide versus Dex? Can doses or schedules of lenalidomide and/or Dex be adjusted to preserve their synergistic direct proapoptotic activity against MM cells, while minimizing Dex-induced immunosuppressive effects? Which clinically applicable marker(s) can identify such potential optimal settings to help individualize the use of these agents?

Until these questions are answered, a key message from this stimulating study is that, in clinical settings where lenalidomide use aims to augment the anti-MM activity of immunotherapeutics, caution should be exercised with concomitant use of potent glucocorticoids.

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Comment on Hosking et al, page 1633

**When the negative is positive**

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In this issue of Blood, Hosking and colleagues report the lack of correlation between genetic variants within the MHC and the risk of ALL.¹

Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer. It is a biologically heterogeneous disease with B-cell precursor ALL as the most common subtype accounting for ~70% of childhood ALL.

There is now conclusive evidence that the risk

Association between SNPs and haplotypes mapping to 6p21 and BCP-ALL risk. The x-axis represents the position of each SNP; the y-axis, P values on a minus logarithmic scale. Cochran-Armitage trend test statistics are shown in black for directly genotyped SNPs and in gray for imputed SNPs in the top panel. Lines in the bottom panel correspond to haplotype test statistics: blue defined by 5 SNPs and red by 12 SNPs. Relative positions of the major HLA genes are also shown. Chromosomal coordinates were derived from the National Center for Biotechnology Information, build 36. See the complete figure in the article by Hosking et al beginning on page 1633.
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