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Not just leukemia: CMV may protect against lymphoma recurrence after allogeneic transplant

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Malignant cells that survive conditioning regimens of allogeneic hematopoietic cell transplantation (HCT) can still be controlled or eliminated immunologically by the donor graft via graft-vs-tumor (GVT) activity. The leading cause of death after transplantation, however, continues to be relapse,[1] indicating that conditioning and GVT are often inadequate. A better understanding of the mechanisms underlying relapse following allogeneic HCT is needed to optimize outcomes for patients.

Although CMV reactivation after allogeneic HCT is a major driver of morbidity, a paradoxical association between CMV and decreased risk of relapse has been documented in numerous single-center analyses.[2-9] Not all studies, however, are in agreement.[10-12] Large registry studies of CMV reactivation in allogeneic HCT donors-recipient have produced conflicting results regarding associations with leukemic relapse. A recent EBMT study of 7,731 patients found that CMV reactivation was associated with improved leukemia-free survival.[13] However, a recent CIBMTR study of 9,469 patients found that CMV reactivation was not associated with attenuation in risk for leukemia relapse.[14] Thus, an association between CMV reactivation and a reduced risk of relapse, focused primarily on leukemia, has been reported by several groups but remains controversial. Heterogeneity in CMV-detection methods, conditioning intensity, graft sources, and T-cell depletion have complicated comparisons across studies.

In this issue of *Leukemia and Lymphoma*, Koldehoff et al. extend their previous observations[5] to now evaluate outcomes in patients with lymphoma.[15] They examined 136 patients with non-Hodgkin lymphoma (NHL) who underwent allogeneic HCT at their center from 2000 to 2014. Of all the patients, 97 were at high risk for CMV reactivation by virtue of seropositivity of donors and/or recipients. A total of 54 patients experienced CMV activation (53 were seropositive) and were preemptively treated, most commonly with ganciclovir or valganciclovir, and less commonly with foscarnet or cidofovir. This subset of patients had a 41% lower 5-year relapse incidence (22% vs 38%, $p<0.013$). The association remained significant after adjustment for a variety of clinical factors including development of acute GVHD, differences in conditioning, disease stage, and patient age ($p<0.014$). A particularly dramatic reduction in relapse incidence was seen in the subset of patients that did not receive anti-thymocyte globulin ($n=78$, 87% reduction, $p<0.05$), suggesting that CMV activation could be modulating T-cell- or NK-cell-mediated responses against lymphoma. In contrast to previous studies, CMV activation was not significantly associated with an increase in non-relapse mortality but did trend in this direction, leading to no change

in overall survival. Why previous studies failed to show a significant negative association with lymphoma relapse [7,16] is an open question but could be related to differences in laboratory techniques used to define CMV reactivation.

A variety of potential explanations can be invoked for the association observed in this retrospective study. One is that a causal relationship exists between CMV reactivation and reduced lymphoma relapse. First, it is possible that lymphoma cells might themselves be infected and lysed by CMV as infection of human lymphocytes by CMV has been reported previously.[17] Alternatively, bystander effects of CMV therapy could be mediating anti-neoplastic responses. While ganciclovir therapy does not appear to be effective against leukemic cells,[7] foscarnet therapy has been reported to be linked with anti-lymphoma effects.[18]

CMV reactivation could also be linked to reduced relapse through augmentation of anti-lymphoma immunity. CMV reactivation has been linked with development of acute GVHD, [19] which is biologically related to GVT. Lymphomas are particularly susceptible to GVT activity.[20-22] CMV has been shown to mediate major effects on the T-cell repertoire, with CMV specificity accounting for 10-30% of circulating memory T cells in healthy seropositive individuals.[23] Post-HCT, T-cell responses to CMV can lead to gaps in the non-CMV-specific repertoire.[24] Intriguingly, a subpopulation of $\gamma\delta$ T cells elicited by CMV reactivation in transplant recipients was shown to cross-recognize both CMV and leukemic blasts.[25] CMV reactivation may also downregulate expression of HLA class I in malignant cells, rendering them vulnerable to NK-cell responses, in particular by the NKG2C⁺ population of NK cells.[26-28] NK cells are well-known contributors to GVT in myeloid diseases,[29] but recent evidence now suggests that NK cells may also be important for graft-versus-lymphoma activity as well.[30]

Alternatively, CMV reactivation could be augmenting T_H1 immune responses in a generalized manner.[31] In a series of studies of transplanted mice bearing B cell lymphomas, CMV could trigger an antitumoral effect that was independent of direct oncolysis, which has been proposed to involve IL-15 signaling.[32-34] Of potential relevance is a recent report that NKG2C⁺ NK cells from CMV-seropositive individuals exhibit increased cytotoxicity compared to those from seronegative individuals, and that IL-15 preferentially expands and potentiates the cytotoxicity of this group of NK cells from CMV-seropositive patients.[28]

Finally, an alternative possibility is that CMV reactivation is not causally linked with reduced relapse but is rather a manifestation or a biomarker of GVT effects. Inflammation generally, and TNF α in particular, have been shown to be triggers for CMV reactivation.[35] Thus, CMV reactivation might be a consequence of either GVT or GVHD responses, an idea supported by the observation that allogeneic stimulation of PBMCs can also reactivate the virus.[36]

In conclusion, one might ask whether the observations of this study can potentially have an impact on patient management. The robustness of these findings has yet to be confirmed, ideally in a multicenter, prospective manner. Additionally, until potential mechanisms are

uncovered that mediate any anti-lymphoma effects of CMV reactivation, how these association might change practice remains to be seen.

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