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EDITORIAL COMMENTARY

Viral Load Kinetics: A Way to Assess Cumulative Effects of Cytomegalovirus on Hematopoietic Stem Cell Transplant Recipients

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(See the Major Article by Stern et al, on pages 620–31.)

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Cytomegalovirus (CMV) has been associated with significant morbidity in hematopoietic stem cell transplant (HSCT) recipients, both via direct effects (DNAemia, end organ disease) and indirect effects (increased risks for other viral and/or fungal infections, graft-vs-host disease [GVHD]) [1, 2]. Predicting its impact on overall survival and nonrelapse mortality post-HSCT has been the focus of many studies. However, understanding cumulative morbidity associated with infections is difficult, as time to first event analyses do not account for recurrent events, and estimates can be biased without controlling for death [3]. Moreover, CMV DNAemia remains a risk factor for overall and non-relapse-related mortality despite institution of a preemptive therapy approach [1].

In this issue of *The Journal of Infectious Diseases*, Stern et al report a study of CMV outcomes in a large single-center HSCT population managed with preemptive therapy, and overcame these limitations by using the "average area under the curve" (AAUC) as a quantitative indicator of CMV load over time, a much more informative tool for cumulative morbidity than time to first DNAemia, or simply the percentage of patients who develop CMV DNAemia and/or end organ disease [4]. This tool incorporates not only the amplitude of DNAemia, but the total duration as well [4–7]. AAUC has been investigated for other double-stranded DNA viruses and has been shown to correlate with increased overall mortality post-HSCT; higher viral load (VL) at onset of DNAemia was associated with more persistent episodes, end-organ disease, and higher mortality [5].

The authors demonstrate effectively that the outcomes associated with CMV are quite different, depending on the patient phenotype as well as the magnitude and duration of CMV DNAemia, and they classified patients based on episodes of CMV DNAemia before day 100 post-HSCT. The "noncontrollers" (higher VL and longer CMV DNAemia) had significantly lower overall survival and higher nonrelapse mortality as compared with all others falling into lower quartiles ("controllers") as well as those defined as "elite controllers" and D^-/R^-; these findings persisted even after adjusting for other covariates. Not surprisingly, HLA-mismatched and T-cell–depleted (TCD) transplants were found to be predictive of "noncontroller" status, while CMV-seropositive donor status was found to be protective. A beneficial effect of donor-seropositive status has been noted in other studies, particularly in unrelated-donor HSCT [8].

The median $CD4^+$ count for both TCD and unmodified HSCT was lower for the noncontrollers, suggesting perhaps that this group of patients has an overall poorer immune status compared to others, rendering them at risk for both CMV and non-CMV infections. Further supporting this is the fact noncontrollers had more deaths due to infections in general when compared to other groups. Even though CMV replication significantly stimulates T-cell function [9], it is also known to be immunosuppressive and increases risks for other infections [2]. Hence, it remains difficult to discern whether lower overall survival and higher nonrelapse mortality in noncontrollers is truly related to CMV, or mainly a reflection of a poor host in whom other factors may play a role.

Incorporating CMV viral load dynamics in a study population with a large sample size, and including assessment of immune reconstitution (including $CD4^+$ counts), adds to a strong study design. Although the overall cohort is large, it is also quite heterogeneous. Almost half of patients had T-cell–depleted HSCT. Approximately 90% of all HSCTs in this cohort were peripheral blood stem cell transplants; graft source may affect GVHD risk [10]. GVHD, in turn, is associated with increased risks for infections including CMV [11]. Indeed, in the study by Stern et al,

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acute GVHD episodes were more frequent in noncontrollers; however, multivariable analyses showed that noncontrollers remained at high risk for mortality even after adjusting for TCD and GVHD. This study did not consider CMV episodes beyond day 100; although rare, these may still influence nonrelapse mortality at 1 year. The increasing use of letermovir prophylaxis may alter this dynamic, whereby CMV episodes might be more frequently late-onset in the future [12].

This study further supports the idea that CMV viral kinetics have a direct relationship with post-HSCT outcomes and should be incorporated as a tool when assessing treatment strategies. Despite the implementation and success of preemptive approaches to CMV DNAemia, it remains an independent risk factor for poor outcomes. This study identifies a group of CMV noncontrollers as a particularly vulnerable group, deserving of further study in terms of preventive interventions. The potential benefits of universal prophylaxis for CMV post-HSCT with newer nonmyelosuppressive agents, such as letermovir, should be assessed in larger clinical trials for this subgroup of noncontrollers. Moreover, a predictive scoring tool could be developed to allow for more objective assessment of patients at higher risk, who may benefit from enhanced prevention strategies. In summary, Stern and colleagues have made an important contribution toward our understanding of cumulative morbidity from CMV, especially in the most vulnerable patients.

Notes

Potential conflicts of interest. All authors: No reported conflicts of interest.

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