The Complexity of Latent Cytomegalovirus Infection in Stem Cell Donors

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(See the Major Article by Ljungman et al on pages 473–81.)

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In solid organ transplant and in stem cell transplant, the impact of the cytomegalovirus (CMV) serologic status of both the donor and recipient have been the subject of intense scrutiny [1, 2]. In both types of transplants, it has been clear that CMV status can play a significant role in the outcome. In solid organ transplant, CMV donor seropositivity has been well established to lead to an increase in mortality, especially among CMV-seronegative recipients [3]. In addition, CMV-seropositive donors have been associated with an increased risk of bacterial and fungal infections, as well as an increase in graft loss [3–5].

In contrast to solid organ transplant, the impact of donor and recipient CMV serostatus in stem cell transplant has been more controversial, and it is likely much more complicated from a pathophysiologic perspective as the donor potentially provides both a risk of CMV transmission as well as a potential benefit for providing T cells with preexisting immunity from the transplant [1, 6, 7].

The article by Ljungman et al in this issue of Clinical Infectious Diseases examines the impact of donor CMV serostatus on outcome in allogeneic stem cell transplant in Europe, analyzing the European Group for Blood and Marrow Transplantation (EBMT) database [8]. It is an important contribution by virtue of the number of patients (>49,000) analyzed and the span of time (1992–2008) explored, during which new transplant practices, such as conditioning regimen, immunosuppression, and diagnosis and treatment of CMV infection have been developed. The large sample size of the EBMT gives extraordinary power to the analyses and offers new insight into the role of the CMV donor and the interaction of the donor with other factors that may have an adverse impact on the outcome of stem cell transplants.

The controversy on the impact of donor CMV serostatus in stem cell transplant has been due to the presence of several contrasting studies. In data from the US National Marrow Donor Program (NMDP) from 1987 to 1999, donor age and human leukocyte antigen (HLA) mismatch, but not donor CMV serostatus, were associated with increased transplant-associated mortality [9]. In general, CMV-seropositive recipients had a poorer outcome, but CMV donor seropositivity did not contribute to an increased risk of death in the CMV-seropositive recipient. Studies by the EBMT published around the same time stood in contrast with these data for HLA-identical siblings, although examination of the subset of CMV-seropositive recipients of stem cells from CMV-seronegative recipients demonstrated higher transplant-related mortality compared with those given CMV-seropositive stem cells [10]. Explanations have included the possible interaction of CMV donor status with disease state leading to transplant, the possible confounding effects of some patients in the analysis being from an era prior to the introduction of ganciclovir, and the possible influence of T-cell depletion or mismatched transplants, which were not part of the analysis of the NMDP dataset. Another single-center study in the era of potentially effective prophylaxis and treatment for CMV infection did not find any association with mortality in the seropositive recipient, but did in the seronegative recipient [11]. It should be pointed out that all the patients in this single-center cohort had unrelated donors and were mismatched.

The reason CMV has the potential to increase mortality is due to the direct effects of the virus, as well as the indirect effects, including bacterial infections,
fungal infections, and development of graft-vs-host disease [12]. We know that CMV-seronegative patients who receive CMV-seronegative stem cells have a better survival than either CMV-seropositive recipients (regardless of CMV donor status) or those who receive a CMV-seropositive donor.

Paradoxically, there is evidence that CMV-seronegative donors can have an adverse impact on CMV-seropositive recipients. Such donors are associated with delayed CMV-specific immune reconstitution, and are associated with the need for multiple treatment courses of CMV viremia and the development of late-onset CMV disease [13, 14]. Despite these data, the current analysis by Ljungman et al demonstrates no adverse impact of a CMV-seronegative donor on CMV-seropositive recipients [8]. The authors postulate an interaction between CMV serologic status and conditioning regimen. When accounting for such an interaction, they demonstrated a protective effect of CMV donor seropositivity with improved survival in patients receiving myeloablative conditioning. The authors postulate that this effect may be due to retention of CMV-specific immune responses in those who have a reduced-intensity conditioning regimen, which preserves T-cell responses, whereas in those with a myeloablative regimen, such an effect would be attenuated or absent.

The strengths of the EBMT study are the power of large numbers, which allows examination of a number of potential interactions within subgroups. Such large multinational databases also allow generalizability. Although there are limitations such as misclassification bias for certain variables, or missing values, the power of the large number of patients for whom there is information gives the study extraordinary power, and can lead to additional hypothesis generation for future studies. Clearly, CMV continues to play a major role in transplant. The EBMT analysis sheds some light on how CMV donor serostatus may interact with the other variables known to affect outcome and mortality in stem cell transplant.

Note

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