

CMV: a warrior against leukemia?

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In this issue of *Blood*, Green et al provide additional information supporting that cytomegalovirus (CMV) reduces leukemia relapse after allogeneic stem cell transplantation.¹

CMV has been called the troll of transplantation mainly due to the high mortality in CMV pneumonia early in the development of bone marrow transplantation. Since then, very substantial improvements in CMV management have been achieved primarily by the development of rapid and sensitive diagnostic techniques allowing for the use of preemptive antiviral therapy resulting in lower rates of CMV disease. CMV has also been associated with indirect effects, including being immunosuppressive and thereby increasing the risk for bacterial and fungal infections.

Almost 2 decades ago, Lönnqvist et al reported that CMV infections in a small cohort study were associated with a decreased relapse risk in acute leukemia.² In this issue of *Blood*, Green et al report on a large cohort of allogeneic stem cell transplantation (SCT) recipients having undergone transplantation for different hematologic malignancies. They found a reduction in relapse risk both at day 100 and at 1 year in the entire cohort.¹

Looking at the separate diseases, there was a significant reduction only for acute myeloid leukemia (AML) at 100 days and a borderline significance at 1 year. This study is an extension of a study by Elmaagacli et al, who reported a significant risk reduction by CMV infection on relapse in AML patients undergoing myeloablative allogeneic SCT from either HLA-identical sibling donors or well-matched unrelated donors.³ In addition, Ito et al also reported a decreased relapse risk in patients with CML,⁴ an observation not verified in the study by Green et al.

How can CMV have an effect on the risk of relapse after allogeneic SCT? It seems to be due to CMV reactivation by itself because there was no effect by CMV serological status. Instead, Green et al showed, surprisingly, that recipient CMV seropositivity was an

independent risk factor for early relapse in acute leukemia and lymphoma. There was also no significant effect of CMV primary infection in CMV-seronegative recipients. Thus, the effect on relapse was limited to the group of seropositive patients who reactivated CMV.

There are several possibilities for this finding. It was shown that allogeneic stimulation can get CMV to reactivate from latency.⁵ Such an allogeneic effect might also influence the relapse risk. However, in both the study by Green et al and Elmaagacli et al, the decreased risk of relapse was independent of acute graft-versus-host disease (GVHD). Furthermore, the effect was independent of chronic GVHD in the Elmaagacli study, and Green et al found the strongest reduction in relapse risk early after SCT.

Could CMV have a direct antileukemic effect by infecting leukemic stem cells? Studies performed many years ago showed that CMV can infect CD33-positive hematopoietic progenitors.⁶ However, no data exist supporting this hypothesis.

Another possible explanation is that the effect is mediated through stimulation and expansion of CMV-specific donor T cells. This was not supported by the findings in the study by Green et al because there was no difference in CMV-seropositive patients of donor serological status. In addition, there is a report by Thomson et al showing no effect of adoptive immunotherapy with CMV-specific T cells on the risk of relapse.⁷ However, a recently published study showed that $\gamma\delta$ T cells elicited by CMV reactivation after allogeneic SCT were able to crossrecognize both CMV-infected cells and primary leukemic blasts.⁸ Given the current existing information, this seems like one of the most likely explanations of the effect of CMV reactivation on relapse.

Green et al suggest that the effect could be mediated through natural killer (NK) cells. It

was shown that CMV has strong effects on the NK cell KIR-receptor repertoire and NK cells are one of the earliest cell types regenerating after allogeneic SCT. The pattern of stronger effects on relapse of AML compared with acute lymphoblastic leukemia supports this hypothesis.

Besides the interesting question regarding the mechanism of the protective effect, the clinically important question is whether these findings should influence patient management. Preemptive antiviral therapy, the currently most-used strategy for CMV management, is likely to have limited impact on the risk of relapse because it is based on the detection of viral replication. Whether it would make a difference for when in the course of a CMV replication episode antiviral therapy is initiated is unclear. Elmaagacli et al used a strict definition of pp65 antigenemia requiring a high number of pp65-positive cells in 2 consecutive samples. However, there was no impact of the number of pp65-positive cells in the study by Green et al. It should be recognized that most centers today use quantitative polymerase chain reaction for CMV monitoring, thereby intervening on a lower CMV viral load and allowing less CMV antigen exposure. The situation might be different if an antiviral drug more or less completely preventing CMV replication is used. Until now, there has been no prophylactic agent against CMV that is both highly effective and safe. Maribavir was the first drug tested in a placebo-controlled trial but failed to reach the primary end point of preventing CMV disease.⁹ Two new antivirals with high efficacy against CMV in vitro and positive results from phase 2 studies, letermovir and CMX-001, are likely to enter phase 3 in the near future. Another interesting development is the recent results from a phase 2 study of a CMV vaccine able to stimulate the specific immune responses to CMV.¹⁰ Because phase 3 studies most likely will be placebo controlled with preemptive therapy used in both arms, these studies might give further insight into the impact of CMV replication on relapse. However, at the end of the day, the results on overall survival will decide which is the optimal strategy. In this aspect, the finding by Green et al that CMV is still associated with an increased risk of nonrelapse mortality and thereby an unchanged overall survival supports that we need additional, preferably controlled studies

to assess the influence of CMV infection on SCT outcome.

Conflict-of-interest disclosure: P.L. has been an advisor for Viropharma, AiCuris, and Astellas. ■

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