CMV Delays Relapse But Does Not Provide Long-Term Survival Benefits

July 15, 2013

G Brennan

Cytomegalovirus (CMV) is a significant source of morbidity in patients with hematologic malignancies post-transplant. Like other herpesviruses, CMV is a life-long infection that is controlled by the immune system. When the immune system is compromised, for instance after hematopoietic stem cell transplant, the virus is no longer controlled and can reactivate, producing more virus to infect and destroy cells. However, some studies have associated CMV reactivation post-transplant with decreased rates of cancer relapse (Lonnqvist, 1986), although some subsequent studies have yielded conflicting results (Remberger, 2002). In a recent study published in Blood, Drs. Margaret L. Green and Michael Boeckh (Vaccine and Infectious Disease Division), along with collaborators from the Fred Hutchinson Cancer Research Center and the University of Washington, evaluate a large cohort of patients treated at the FHCRC to address this conflict. Their data shows that although CMV reactivation provided modest protection for patients with acute myeloid leukemia (AML) in the first year after treatment, CMV reactivation was also associated with a risk of non-relapse mortality. This study supports the current practice of CMV treatment to limit reactivation.

In the current study, 2566 patients with various hematologic malignancies were enrolled. Approximately 65% of all patients had a risk of CMV reactivation, either because they were seropositive (R+) or because they received a transplant from a seropositive donor (D+). Over the course of the study, 36.1% of all patients had CMV reactivation, and 11.6% were classified as “high” reactivation. Consistent with FHCRC treatment regimens, any patient who tested positive for CMV reactivation was treated with ganciclovir or foscarnet, which blocks CMV replication. CMV seropositivity and reactivation status was similar across all disease groups.

In univariate regression models, CMV reactivation did not decrease the risk of relapse for patients. However, after adjusting for variables such as donor and recipient CMV serostatus, patients with AML, but not other malignancies, had a significantly lower risk of relapse after early CMV reactivation (adjusted HR=0.56, 95% CI 0.3-0.9, p=0.02). This effect was not due to cytotoxicity mediated by ganciclovir treatment, and higher levels of CMV reactivation did not provide greater protection. However, this protective effect was not observed after one year post-transplant. Paradoxically, transplant recipients who were CMV seropositive prior to transplantation had a two-

fold increased risk of relapse by day 100 across the cohort, and CMV reactivation was associated with a 31% increase in non-relapse related mortality (adjusted HR 1.31, 95% CI 1.1-1.6, p=0.02).

Green, et al. demonstrate that early CMV reactivation in AML patients inhibits relapse in the first year after transplantation. This protective effect is not due to ganciclovir treatment; however, the biological mechanism remains unclear. The authors propose an intriguing hypothesis that natural killer (NK) cell upregulation as a result of CMV reactivation may increase NK cell killing against residual tumor cells. If true, this hypothesis may represent an exciting new area of post-transplant therapy. However, the significant increase in non-relapse mortality observed in this study strongly supports current treatment regimens to limit CMV replication in these patients.

Green ML, Leisenring WM, Xie H, Walter RB, Mielcarek M, Sandmaier BM, Riddell SR, Boeckh M. 2013. Blood. Epub ahead of print, doi:10.1182/blood-2013-02-487074.

See also: Lönnqvist B, Ringdèn O, Ljungman P, Wahren B, Gahrton G. 1986. Reduced risk of recurrent leukaemia in bone marrow transplant recipients after cytomegalovirus infection.Br J Haematol. 63(4):671-9.

See also: Remberger M, Ringdén O. 2002. Survival after bone-marrow transplantation. Lancet. 359(9309):888.

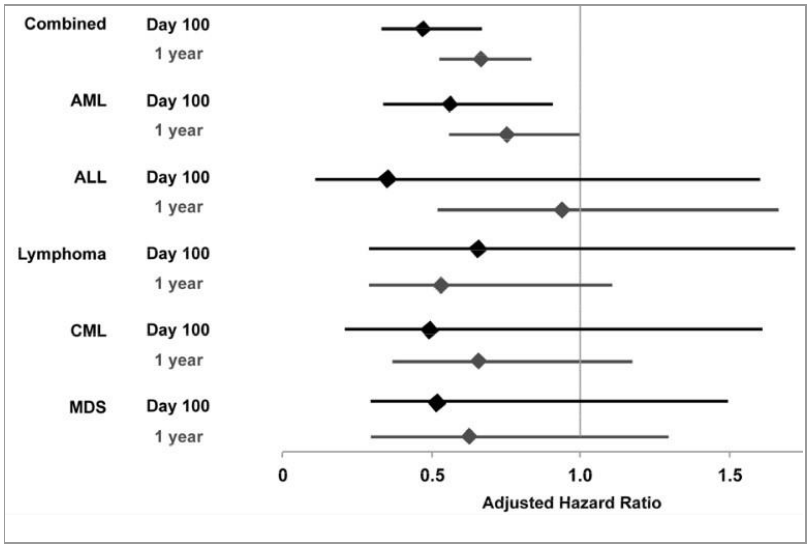

Image modified from Green et al., 2013.

The hazard ratio for relapse at day 100 and 1 year post-transplant for patients with early CMV reactivation displayed as a whisker plot.