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Commentary

Cytomegalovirus: Why Viral Dynamics Matter

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Contrary to bacterial replicating kinetics, where the doubling time varies considerably but often is measured in minutes or hours, viral replication kinetics is calculated in days. A new study by Isabelle Lodding and colleagues in E-Biomedicine attempts to calculate the doubling time of cytomegalovirus (CMV) in a cohort of solid organ and stem cell recipients (Lodding et al., 2015). Why does the doubling time of CMV matter? This number is of great interest to the transplant specialist, as the preemptive treatment approach relies on the detection of replicating CMV in blood before disease occurs. Regular determination of quantitative CMV PCR testing allows selecting those patients with reactivation of CMV in need of a preemptive treatment. Often, a quantitative CMV copy threshold in blood is used to start antiviral treatment. Neither the optimal frequency of CMV testing nor the ideal source of CMV PCR (whole blood, or plasma), nor the optimal threshold has been established. Thus, protocols between transplant centers vary. The recently published updated international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation recommended weekly testing for 3–4 months, with moderate evidence (Kotton et al., 2013). For most centers, however, it would be very difficult to adhere to such a tight schedule, in particular later after transplantation. Therefore, a precise knowledge of the doubling time would allow to safely widen the interval between CMV PCR testing, without an increase in CMV disease episodes. The main finding of the study by Lodding and colleagues is a CMV doubling time of 4.3 days (median, IQR 2.5–7.8), which in contrast to earlier studies is considerably longer. Neither the donor–recipient CMV sero-constellation nor the type of transplant did influence these results. Earlier studies by V. Emery and P. Griffiths in bone marrow transplant patients estimated a shorter doubling time of CMV of 1.5 days (median, range 0.38–4.7) (Emery et al., 1999). Similar doubling times were calculated in a cohort of liver transplant recipients (2 days (median, 0.1–69)) (Nebbia et al., 2007). Many factors may have influenced these different estimates, including the intensity of immunosuppression, the type of sample used for CMV PCR detection, frequency of measurement, type of transplantation, or percentage of patients at high risk for CMV reactivation. While some are less likely than other to play a role, data on the influence of these factors on the doubling time are conflicting.

Interestingly, in their simulation model, Lodding and colleagues were able to predict their real rate of recipients with a high CMV viral load (1.4%, arbitrarily set at >18,200 IU/mL) with the assumption of their lower doubling time of 4.3 days. Using a shorter doubling time of 1.3 days, the proportion of patient with a high viral load would have been 11%. The authors suggest that in cohorts with comparable doubling times, the screening interval can be safely extended. While this may decrease the cost burden due to less visits and screening costs, it should be emphasized that the most important goal is to reduce symptomatic CMV episodes in these vulnerable patients. We and others have shown that many factors including as strict adherence to a guideline with timely start of antiviral therapy in case of reactivation contribute to the success of the preemptive approach (Greiner et al., 2012). Of note, the number of patients with CMV disease was rather high and reached 31% during the observation time in the study by Lodding and colleagues.

The basis of any informed decision on how to adapt the screening schedule is a precise knowledge of the rate of CMV disease episodes in its own institution. Such information is crucial to recognize a relevant increase in the rate of CMV disease once changes of the preemptive protocol have been implemented. Any change in clinical routine should be accompanied by a careful evaluation of its effect on the pertinent endpoints. The importance of the role of carefully maintained cohorts such as the one built and used to by Lodding and colleagues to answer such questions in a real-life environment cannot be overstated.

Disclosure

The author declares no conflicts of interest.

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