Response

Human cytomegalovirus DNAemia and preemptive treatment of HCMV infection in children receiving hematopoietic stem-cell transplantation

We thank Cesaro and colleagues for having carefully read our paper and for raising concerns that we have now the opportunity to answer. Unfortunately, our manuscript had to be shortened as requested by the reviewers, but questions unsettled in this brief report can now be addressed as follows. (1) Although it is generally assumed that polymerase chain reaction (PCR) has a greater sensitivity than antigenemia, in our extensive experience we have observed that this is not the case for both solid organ and hematopoietic stem-cell transplantation (HSCT) recipients,[1-3] where time to virus detection by the 2 assays was not found to be significantly different. (2) The criterion for discontinuing antiviral treatment was virus clearance from blood (that is, negative PCR in the relevant arm): this did not lead to more prolonged treatment in the DNAemia arm. In this respect, delayed antigenemia clearance (or even an initial paradoxical antigenemia rise) is more likely to be detected during ganciclovir treatment of human cytomegalovirus (HCMV) infection.[4] This is due to the biologic characteristics of pp65, which is synthesized in excess by HCMV-infected endothelial cells before transfer to leukocytes.[5,6] (3) In the cohort examined in our study,[2] altered viral clearance was observed in 10 of 44 of the patients treated. Three patients (1 in the DNAemia and 2 in the antigenemia arm) had an initial paradoxical rise in antigenemia, which was dissociated from a prompt DNAemia decrease. The other 7 patients (3 in the DNAemia and 4 in the antigenemia arm) showed an initial increase in both antigenemia and DNAemia[4,7] levels after initiation of therapy. All 7 patients had grade 2-IV acute graft-versus-host disease (GVHD), which was treated with high-dosage steroid therapy. A multivariate analysis identified steroid therapy as the only parameter significantly associated with virus persistence in blood. In these 7 patients, median duration of therapy (35 days, range 16-69 days) was significantly longer ($P = .002$) than in patients showing a prompt decrease in levels of different viral parameters measured (13 days, range 5-66 days). However, because acute GVHD incidence was not different between the 2 arms, this difference affected neither the number of patients treated nor treatment duration. (4) As Cesaro and colleagues correctly point out, the reduced number of patients treated was due mostly to the adoption of a cutoff in the DNAemia arm instead of first virus detection, as in the antigenemia arm. (5) We disagree with Cesaro and colleagues' argument against our conclusion on the safety of the DNA cutoff for starting preemptive therapy. The number of patients enrolled is not low. Moreover, in agreement with another investigation,[8] the DNAemia cutoff we chose was shown to be equally safe in a higher-risk population of adult patients receiving HSCT.[3]

In conclusion, DNAemia is preferable over antigenemia because it better reflects actual HCMV replication, and the adoption of a cutoff for starting preemptive therapy avoids unnecessary treatment of patients spontaneously clearing HCMV infection by an early HCMV-specific, T-cell immune reconstitution.

Giuseppe Gerna, Daniele Lilleri, and Franco Locatelli

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Correspondence: Giuseppe Gerna, Servizio di Virologia, Fondazione IRCCS Policlinico San Matteo, Via Taramelli 5, 27100 Pavia, Italia; e-mail: g.gerna@smatteo.pv.it

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