To the editor:

Valganciclovir versus valaciclovir for prevention of alemtuzumab-induced cytomegalovirus reactivation: what are the implications for routine clinical practice?

I read with interest the recently published study by O’Brien et al1 on valganciclovir versus valaciclovir in prevention of cytomegalovirus (CMV) reactivation in patients with lymphoid malignancies treated with alemtuzumab-containing regimens. The study was terminated early after enrollment of 40 patients due to CMV reactivation in 7 of 20 patients on valaciclovir versus 0 of 20 on valganciclovir, with the conclusion that valganciclovir is highly efficient in CMV prevention in this setting. As this topic is extremely important due to an increasing use of alemtuzumab in patients with chronic lymphocytic leukemia (CLL), I would like to comment on some controversial issues, especially with regard to routine clinical management in this setting.

Although reported as a randomized study, I believe that the treatment arms were not very comparable. Twenty-five percent of patients had lymphoid tumors other than CLL with various degree of immunosuppression and resulting susceptibility to CMV reactivation (eg, acute lymphoblastic leukemia, marginal zone leukemia, T-cell malignancies, etc) and unequal distribution within the valganciclovir versus valaciclovir group. Monotherapy with alemtuzumab for CLL (the only FDA-approved and therefore routinely used indication) was used in 5 of 40 patients only. The other 4 regimens used in the study were unequally distributed within antiviral treatment arms, purely experimental, and likely to cause significant bias on the rate of CMV reactivation given their immunosuppressive potential.

With regard to the dosage of studied anti-CMV agents, I believe it would be more appropriate to use a comparable dose of valganciclovir versus valaciclovir rather than 900 mg of valganciclovir versus 500 mg of valaciclovir. The reported bioavailability is 60% for valganciclovir and 50% to 70% for valaciclovir2-5; thus, patients receiving valganciclovir were exposed to 50% higher level of the active drug than those on valaciclovir. Obviously it is then hard to distinguish whether the lower rate of CMV reactivation in the valganciclovir arm was caused by better efficacy or merely by higher dose.

Hematologic toxicity of valganciclovir is a well-known side effect. Unfortunately, the actual incidence of neutropenia and thrombocytopenia related to antiviral treatment was impossible to report (as the authors mention themselves) due to severe myelosuppression already caused by the aggressive anticancer regimens.

The assay used by the authors for CMV detection (pp65 antigenemia) is considered less sensitive in comparison to nowadays widely used polymerase chain reaction (PCR), especially in patients with leukopenia.6 One could then ask whether this method was an ideal choice for patients with expected high rates of leukopenia and whether the more sensitive PCR method could detect CMV in a higher number of patients and affect final results. On the other hand, CMV reactivation in alemtuzumab-treated CLL patients appears to be less dangerous than in patients after allogeneic stem cell transplantation. For example, there were only 3 cases of CMV pneumonia (one fatal) in almost 600 reported patients.7-9 Finally, due to lack of evidence it is currently unclear whether asymptomatic CMV low positivity detected by a sensitive assay in these patients necessarily warrants alemtuzumab interruption and preemptive anti-CMV treatment or whether watchful waiting with repeated CMV measurements could be sufficient; or whether weekly CMV surveillance is actually necessary at all.

In conclusion, the study by O’Brien et al is indeed very important and useful; however, the abovementioned problems in my opinion rather limit its impact on daily practice. Therefore, I believe that larger studies addressing the efficacy, safety, and cost-effectivity issues are necessary before routine clinical use of valganciclovir for CMV prevention in patients with CLL treated with alemtuzumab can be recommended.

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References
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