Aerosolized Ribavirin for Patients With Cancer and Respiratory Syncytial Virus Infection

TO THE EDITOR—In a recent issue of the Journal of Infectious Diseases, Chemaly et al report the results of their randomized clinical trial, which compared an intermittent (ISR) versus a continuous dosing schedule (CSR) of ribavirin in patients with respiratory syncytial virus (RSV) infection and cancer [1]. The premature discontinuation of another randomized study because of slow accrual after 5 years [2] demonstrates the challenges associated with clinical research in this field. Thus, Chemaly et al should be congratulated for successfully accomplishing this difficult trial.

The authors claim, as the main result of the study, that ISR was more efficacious than CSR in the prevention of progression from upper respiratory tract to lower respiratory tract RSV infection. Unfortunately, this result is not plausible from a clinical perspective, since daily doses of ribavirin (6 g) were identical in both groups, and tolerability and safety were also not different. The authors hypothesize that the higher success rate in the ISR arm could be explained by better compliance, but their tolerability and safety findings do not substantiate this explanation: 1 discontinuation occurred in each arm, and no other data supporting their hypothesis are provided.

We challenge the authors’ statement regarding the superior efficacy of ISR. The authors have put together an impressive list of patient risk factors: coinfections were more common in the CSR group (P = .03); the rate of graft versus host disease, which is associated with increased immunosuppression, was (not significantly) higher in the CSR group; and the rate of autologous transplantation was (not significantly) higher in the ISR group. Although we cannot claim that bias introduced by these factors influenced the study’s main result, the list of items demonstrates several sources for bias. The randomization process was changed to adapted randomization after enrollment of 10 patients. Estimating a priori probabilities from only 10 treated patients in a highly variable population is prone to bias but critical for all further computations. We challenge the use and value of the a priori and a posteriori probabilities given by the authors in this complicated and highly variable patient cohort. The adaptive randomization process is very sensitive to the characteristics of the first few patients included, and so are all calculations of the accompanying probabilities. No other result from the trial, such as the finding that mortality was the most important end point or that viral shedding was a surrogate marker, supports the authors’ claim. In addition, the crude rates of progression in both groups are not statistically different.

Since no completed clinical trial comparing aerosolized ribavirin with placebo is available, it is still not known whether ribavirin in any dosing form is beneficial in this setting. Although the authors argue that published reports on this issue indicate some efficacy of ribavirin [3], all information relies on noncontrolled studies with varying methodological quality. Others have used oral ribavirin for treatment of RSV infection in adult cancer patients, but again the results are inconclusive [4].

In conclusion, the study by Chemaly et al should not be regarded as proof for the efficacy of aerosolized ribavirin in general or ISR specifically in the treatment of RSV infections in adult cancer patients. Therefore, decisions regarding treatment of RSV infection in these patients should still be made on a case-by-case basis until results of more-rigorous clinical trials are available.

Note

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