Does High-Dose Prophylactic Acyclovir Add Benefit in Allogeneic Marrow Transplant Recipients Receiving Prophylactic or Preemptive Ganciclovir?

To the Editor—Boeckh et al. [1] concluded in a retrospective study that there appears to be no evidence that high-dose acyclovir given for cytomegalovirus (CMV) prophylaxis adds benefit when ganciclovir is given prophylactically or as a preemptive treatment for pp65 antigenemia. This conclusion was based on the analysis of survival and CMV disease incidence from 3 different groups. Group 1 received prophylactic ganciclovir from the time of engraftment until day 100. Group 2 received preemptive ganciclovir on the basis of pp65 antigenemia. Neither of these groups received previous high-dose acyclovir treatment. Group 3 received high-dose acyclovir from day —5 until the time of engraftment and, thereafter, received prophylactic ganciclovir until day 100. Group 1 (prophylactic ganciclovir) served as a “control” for group 3 (high-dose acyclovir plus prophylactic ganciclovir), to assess the role of high-dose acyclovir, but there was no group to compare with group 2 (preemptive ganciclovir).

We disagree with some of the conclusions because, in our opinion, the data presented by Boeckh et al. [1] support only an absence of efficacy of high-dose acyclovir (assessed by the impact on survival and CMV disease incidence) in patients receiving prophylactic ganciclovir.

First, for patients receiving preemptive ganciclovir (group 2), a group with high-dose acyclovir plus preemptive ganciclovir does not exist, to assess the effect of high-dose acyclovir. Therefore, Boeckh et al. [1] provide no data to support the conclusion that high-dose acyclovir does not benefit patients receiving preemptive ganciclovir. In the only published randomized study of high-dose acyclovir [2] (updated in [3]), only conventional virologic tests were used (tissue culture or early antigen detection). Preemptive treatment was used in some of these patients on the basis of viremia. In this setting, high-dose acyclovir significantly reduced the probability and delayed the onset of CMV infection (including viremia) and significantly improved survival. Whether these results would be the same today is not known. Bone marrow–transplant patients currently are being monitored by more-sensible techniques (i.e., antigenemia or detection of CMV DNA by polymerase chain reaction [PCR]), and, as a consequence, more patients are receiving preemptive treatment and are receiving treatment earlier. The only way to assess this problem would be a randomized study comparing patients treated with and without long-term high-dose acyclovir plus preemptive ganciclovir on the basis of antigenemia or detection of CMV DNA by PCR.

Second, high-dose acyclovir in group 3 was probably administered for too short a time to allow an effect on survival and CMV disease incidence. In the study by Prentice et al. [2, 3], high-dose acyclovir was associated with an improvement in survival only when used long term (6 months) and not when used short term (35 days). In a nonrandomized prospective trial [4], 35 days of high-dose acyclovir significantly reduced the risk of CMV disease and improved survival. In the study of Boeckh et al. [1], high-dose acyclovir was given for ~25 days (5 days prior to transplant plus 20 days until engraftment). So, according to Prentice et al. [2, 3] and to the experience of the Seattle group [4], high-dose acyclovir in group 3 was administered for a time far shorter than that necessary to observe a beneficial effect, if one exists.

Third, the effect of high-dose acyclovir on CMV infection incidence was not commented on in the article. High-dose acyclovir has been shown to reduce the risk of CMV infection in patients not receiving prophylactic ganciclovir [2–4]. It would be interesting to know whether this reduction also occurs in patients receiving prophylactic ganciclovir. Although no randomized study has evaluated the influence of a high-dose acyclovir treatment in this setting, there was a remarkable difference in the incidence of CMV infection between the two largest randomized studies of prophylactic ganciclovir (20% [5] vs. 3% [6]). Several differences exist between the studies, but one of the most relevant was the use of high-dose acyclovir only in the study by Goodrich et al. [6], which had the lowest incidence of CMV infection.

Care must be taken before discarding CMV prophylactic regimens, like high-dose acyclovir, that have been shown to improve survival, since we have a poor understanding of the mechanisms involved. Perhaps new trials evaluating the value of high-dose acyclovir in the modern era of preemptive treatment, based on antigenemia or detection of CMV DNA by PCR, would be helpful. On the other hand, prophylactic ganciclovir, which is very effective in the reduction of CMV infection and early CMV disease, has not been shown in a randomized trial to improve survival in bone marrow transplant patients when compared with either a placebo [5, 6] or a preemptive use of ganciclovir [7]. Despite extensive studies of CMV in bone marrow transplant patients, we have much more to learn and to understand. Thus, we think that the controversy regarding the role of high-dose acyclovir in allogeneic stem cell transplants remains open, at least for patients treated without prophylactic ganciclovir.
References


Reply

To the Editor—We agree with Drs. de la Cámara and Fernández-Ranada that prospective randomized trials are the optimal way to address nearly all sticky therapeutic problems. The trials by both Meyers et al. [1] and Prentice et al. [2] were designed to evaluate the prophylactic effect of high-dose acyclovir on herpesvirus suppression. However, ganciclovir has been shown to have better in vitro and in vivo activity than acyclovir for β and γ herpesviruses and nearly equal activity against α herpesviruses (albeit more toxic). Although it could be argued that early high-dose acyclovir might reduce the need for ganciclovir in an antigenemia- or PCR-guided strategy (due to a reduced incidence of antigenemia or DNAemia), our data does not support such an assumption (see below). Therefore, according to nearly all authorities and institutional review boards, there is currently no rationale for doing an equivalence trial, in which one receives high-dose acyclovir followed by ganciclovir. The major purpose of the present study [3] was to determine, retrospectively, whether the decision to discontinue high-dose acyclovir resulted in an adverse outcome (i.e., in a higher mortality and/or in a higher incidence of cytomegalovirus [CMV] disease). Our review suggested that high-dose acyclovir, given from day −5 until engraftment, does not appear to add benefit when ganciclovir is given either at engraftment or for pp65 antigenemia. Thus, at present, our standard regimen uses herpes simplex virus-suppressive doses of acyclovir or valacyclovir for the initial 30 days of transplant, followed by pp65 antigenemia-guided preemptive therapy with ganciclovir.

Drs. de la Cámara and Fernández-Ranada raise the interesting issue as to whether it is valid to compare the group that received pp65 antigenemia–based preemptive ganciclovir with the 2 groups that received ganciclovir at engraftment. The aim of these comparisons was to evaluate different strategies of prevention of CMV disease after allogeneic marrow transplantation. Although we recognize that there was no direct comparison group of patients who received high-dose acyclovir followed by pp65 antigenemia–based preemptive ganciclovir, the strategy of giving ganciclovir for pp65 antigenemia without high-dose acyclovir did not result in a higher mortality than either of the ganciclovir prophylaxis strategies. If anything, there was a trend toward improved long-term outcome with pp65 antigenemia–guided preemptive therapy, presumably because of less toxicity from ganciclovir. Although it is possible that a strategy of high-dose acyclovir until day 28 after transplant (or even longer administration of acyclovir, as used by Prentice et al. [2]) followed by pp65 antigenemia–based preemptive therapy might have resulted in improved survival, this appears improbable to us, given the apparent lack of effect on survival of high-dose acyclovir in combination with ganciclovir prophylaxis at engraftment.

To evaluate whether high-dose acyclovir would reduce the onset of early CMV excretion among patients who were subsequently placed on ganciclovir, we reviewed CMV surveillance cultures from blood, urine, and throat among the 3 groups included in our study [3]. CMV viremia (4.5% [acyclovir-ganciclovir] vs. 5.4% [ganciclovir at engraftment]) and excretion of CMV in urine or throat (or both; 9.8% vs. 8.9%) were not different between recipients of high-dose acyclovir and those who did not receive high-dose acyclovir (figure 1). The overall incidence of CMV infection, as determined by excretion from blood, urine, and throat at engraftment and day 100 after transplant, was 10.5% in acyclovir-ganciclovir patients and 11.6% in recipients of ganciclovir at engraftment without prior high-dose acyclovir. Of interest, there was also no increased CMV infection prior to engraftment in patients who did not receive high-dose acyclovir (9.7% [acyclovir-ganciclovir] vs. 2.7% [ganciclovir]). As one would expect, the patients who received ganciclovir on the basis of pp65 antigenemia had a substantially higher incidence of CMV excretion from blood, urine, and throat (figure 1). The incidence of CMV excretion among recipients of ganciclovir at engraftment with and without prior high-dose acyclovir appears somewhat higher than that reported during our previous trial (i.e., 3% [3]). This