Effect of High-Dose Acyclovir on Survival in Allogeneic Marrow Transplant Recipients Who Received Ganciclovir at Engraftment or for Cytomegalovirus pp65 Antigenemia

Michael Boeckh, Ted A. Gooley, and Raleigh A. Bowden

Fred Hutchinson Cancer Research Center and the University of Washington, Seattle, Washington

This study sought to determine whether high-dose acyclovir improves posttransplant survival in cytomegalovirus (CMV)-seropositive patients when ganciclovir is given for prophylaxis or as early therapy. Three groups were studied: Group 1 (n = 112) received ganciclovir from engraftment without prior acyclovir treatment, group 2 (n = 114) was given ganciclovir for CMV pp65 antigenemia without prior acyclovir, and group 3 (n = 133) received ganciclovir at engraftment with prior intravenous acyclovir (500 mg/m² every 8 h) from day 5 before transplant until engraftment. In a multivariable Cox model, there was no significant difference in the adjusted risk of transplant survival between the groups during the first 2 years after transplant (relative risk for mortality: group 1, 1.0; group 2, 0.75 (95% confidence interval [CI], 0.52–1.1); group 3, 1.04 (95% CI, 0.74–1.47)). The incidence of CMV disease and CMV-related mortality was not significantly different between the groups. Thus, high-dose acyclovir does not appear to improve survival when ganciclovir is given either at engraftment or for CMV pp65 antigenemia.

Two studies have shown improved survival in patients given high-dose acyclovir (500 mg/m² every 8 h) intravenously (iv) from day 5 before transplant (−5) until day 30 after transplant alone or with subsequent oral acyclovir (800 mg 4 times/day until day 210) [1–3]. Despite these positive results, the issue of acyclovir for prevention of cytomegalovirus (CMV) disease remains controversial among stem cell transplant centers [4, 5]. The major reason for this controversy is a poor understanding of the mechanisms of the observed survival benefit. The differences in survival in these studies could not clearly be attributed to a reduction of CMV-associated mortality [1–3]. It has been hypothesized that early suppression of CMV infection or other herpesviruses, such as human herpesvirus 6, during the first month after transplant by iv high-dose acyclovir may be responsible for the observed survival benefit [2, 6]. Other reasons for the controversy include the availability of more potent anti-CMV compounds, such as ganciclovir and foscarnet, the high cost of the proposed acyclovir regimens, especially when added to conflicting results on the efficacy of high-dose acyclovir in human immunodeficiency virus–infected patients [7–10], results in solid organ transplant recipients that show superior efficacy of ganciclovir compared to acyclovir [11], and the lack of efficacy of high-dose acyclovir for prevention of CMV in autologous marrow transplant recipients [12].

It is unclear whether high-dose acyclovir has additional benefit if ganciclovir is given at engraftment or for early treatment based on CMV pp65 antigenemia or polymerase chain reaction (PCR) detection of CMV DNA, the two most common strategies at this time. Because there are no published reports or ongoing controlled studies addressing the issue and because the cost of the proposed acyclovir regimen is substantial, we examined the impact of high-dose iv acyclovir treatment as described by Meyers et al. [1] on transplant survival, CMV-related mortality, and CMV disease in seropositive allogeneic marrow transplant recipients who received either ganciclovir at engraftment or for pp65 antigenemia.

Methods

Patients. Consecutive CMV-seropositive patients of all ages undergoing allogeneic marrow transplantation at the Fred Hutchinson Cancer Research Center between July 1991 and March 1994

Received 6 January 1998; revised 11 May 1998.

Informed consent was obtained from patients or their parents or guardians. Human experimentation guidelines of the US Department of Health and Human Services and of the University of Washington and Fred Hutchinson Cancer Research Center (FHCRC) were followed in the conduct of clinical research. The study was approved by the FHCRC Institutional Review Board.

Grant support: American Cancer Society (RD-361); National Institutes of Health (CA-18029).

Reprints or correspondence: Dr. Michael Boeckh, Fred Hutchinson Cancer Research Center, Program in Infectious Diseases, 1100 Fairview Ave. N. D3-100, Seattle, WA 98109-4417 (mboeckh@fhcrc.org).

The Journal of Infectious Diseases 1998;178:1153–7

© 1998 by the Infectious Diseases Society of America. All rights reserved.

0022–1899/98/7804–0033$02.00
were included in this analysis. Patients received 1 of 3 potential treatment regimens. Group 1 patients received ganciclovir from engraftment (defined as an absolute neutrophil count of $>0.750 \times 10^9/L$ for 2 days) until day 100 after transplant without prior acyclovir treatment. Group 2 patients received ganciclovir (5 mg/kg twice a day for 7 days followed by 5 mg/kg/day) for CMV pp65 antigenemia ($>3$ positive cells in 2 slides) for a minimum of 3 weeks or until 6 days after antigenemia ended, whichever occurred later; treatment was resumed for 2 weeks or until 6 days after cessation of antigenemia if antigenemia recurred before day 80 after transplant. Patients in groups 1 and 2 participated in the randomized trial reported earlier [13]. Group 3 consisted of patients transplanted before the start of the randomized trial who were treated with high-dose acyclovir (500 mg/m$^2$ every 8 h iv) from day 5 before transplant until engraftment (as defined above) and subsequently with ganciclovir (5 mg/kg twice daily for 5 days followed by 5 mg/kg once a day, 6 or 7 days/week) until day 100 after transplant.

Group 3 patients met the same inclusion criteria as those in the prior randomized trial [13] (i.e., engraftment, serum creatinine $<220\, \mu\text{mol/L}$ [2.5 mg/dL], absence of CMV viremia and disease). In groups 1 and 2, acyclovir (250 mg/m$^2$ twice a day) was given to herpes simplex virus (HSV)–seropositive subjects from the start of conditioning until day 30 after transplant. This regimen was previously shown not to affect CMV [14]. The majority of patients received fluconazole (400 mg/kg/day) from conditioning until day 75 after transplant [15].

Definitions. CMV disease was defined as demonstration of virus from visceral sites (lung, gastrointestinal tissue, liver) by culture or histology or in broncholaveolar lavage fluid by culture or direct fluorescent antibodies in the presence of new or changing pulmonary infiltrates [13]. Late CMV disease was defined as disease occurring $>100$ days after transplant. CMV-related death was defined as death occurring within 6 weeks of the diagnosis of CMV disease [13].

Statistical analysis. The primary analysis was performed using a Cox proportional hazard model for patients in each group who met the criteria to start ganciclovir at engraftment as defined in [13]. Because high-dose acyclovir was given before engraftment and may have its major effect during that period, two additional analyses were done. First, transplant survival was compared among patients who were excluded from the primary analysis because they did not meet criteria of engraftment (i.e., due to early death, graft failure, or failure to meet inclusion criteria for the randomized trial). Second, survival was analyzed in all patients transplanted during the study period. For the latter analysis, all patients who received acyclovir (group 3 plus patients who were excluded from the primary analysis) were compared with those who did not receive acyclovir (groups 1 and 2 plus patients who were not eligible for the randomized trial and did not receive acyclovir [13]). This analysis was done because patients in groups 1 and 2 were randomized only at the time of engraftment, and the lack of high-dose acyclovir could have led to a higher rate of early death. Survival analysis estimates were done by the method of Kaplan and Meier. Cox proportional hazards models were fit to analyze risk factors for mortality and CMV disease in patients who fit criteria for inclusion in the primary analysis and for all patients. All $P$ values from the regression models are 2-sided and were derived from the Wald test. No adjustments were made for multiple comparisons.

Results

Patients. In total, 437 patients were transplanted during the study period: 160 received high-dose acyclovir and 277 did not. Of the subjects, 359 engrafted and met criteria to start ganciclovir as defined in [13]. Patients excluded from the primary analysis due to early death or failure to meet inclusion criteria of the randomized trial included 27 (16.9%) of 160 who received high-dose acyclovir and 51 (18.4%) of 277 not given high-dose acyclovir. There was no statistically significant difference between groups 1–3 in age, gender, underlying disease risk, conditioning regimens, graft-versus-host disease (GVHD) prophylaxis, and the proportion of related HLA mismatched and unrelated donors (51%, 51%, 44%, respectively). There was also no significant difference in posttransplant factors, such as time to engraftment (median days 20.5, 21.0, 20.0, respectively) and grade 3–4 GVHD (33%, 35%, 41%, respectively). All patients in groups 1 and 2, and 48% of patients in group 3 received fluconazole prophylaxis.

Survival. Results of a multivariable Cox proportional hazards model to account for known risk factors for transplant mortality (i.e., underlying disease risk [low vs. intermediate vs. high], age [as continuous variable], donor type [matched related vs. mismatched related or unrelated], total body irradiation, CMV donor serostatus, transplant number, and use of fluconazole prophylaxis) are shown in table 1. After adjusting for these factors, there was no evidence of a survival benefit of high-dose acyclovir, either at day 100 or at 2 years after transplant (table 1). Acute GVHD was not included in this model as it is possible that acyclovir is associated with an increase or decrease in this complication that could mask the effect of acyclovir on survival. Nevertheless, when such a model was constructed, the qualitative results were not different (data not shown). The univariable survival estimates in the 3 groups are shown in figure 1A. Figure 1B shows survival curves of all patients who were transplanted during the study period, including those who did not meet criteria for inclusion in the primary analysis. There was no statistically significant difference among excluded patients who did and did not receive high-dose acyclovir. An analysis that included low-risk patients only (age $<40$ years, transplant from a matched-related donor) did not show any hint of a survival benefit among patients who received high-dose acyclovir (data not shown).

CMV disease. The incidence of CMV disease before engraftment was not different between patients who received high-dose acyclovir and those who did not (3/160 [1.9%] vs. 7/277 [2.5%]). There was no statistically significant difference in CMV disease at any time between engraftment and day 400 between groups 1 and 3 (table 1). There was a transient increase of CMV disease among patients who received intermittent pp65 antigenemia–guided ganciclovir compared to ganciclovir at engraftment as reported earlier [13], but there was no statistically significant difference at day 180 and thereafter. CMV-related mortality was not different between the groups during
Table 1. Multivariable Cox proportional hazard model of overall mortality and CMV disease in persons given ganciclovir for prophylaxis or for early therapy.

<table>
<thead>
<tr>
<th></th>
<th>Day 100</th>
<th></th>
<th></th>
<th>2 years</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR (95% CI)</td>
<td>P</td>
<td>RR (95% CI)</td>
<td>P</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Groups 1 + 2 + 3 (n = 359)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At engraftment</td>
<td>No</td>
<td>1.0 (—)</td>
<td>—</td>
<td>1.0 (—)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>For pp65 antigenemia</td>
<td>No</td>
<td>1.14 (0.57–2.31)</td>
<td>.71</td>
<td>0.75 (0.52–1.10)</td>
<td>.14</td>
<td></td>
</tr>
<tr>
<td>At engraftment</td>
<td>Yes</td>
<td>1.39 (0.71–2.72)</td>
<td>.33</td>
<td>1.04 (0.74–1.47)</td>
<td>.81</td>
<td></td>
</tr>
<tr>
<td>CMV disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At engraftment</td>
<td>No</td>
<td>1.0 (—)</td>
<td>—</td>
<td>1.0 (—)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>For pp65 antigenemia</td>
<td>No</td>
<td>5.55 (1.62–19.04)</td>
<td>.007</td>
<td>1.38 (0.74–2.57)</td>
<td>.31</td>
<td></td>
</tr>
<tr>
<td>At engraftment</td>
<td>Yes</td>
<td>0.58 (0.10–3.45)</td>
<td>.55</td>
<td>0.86 (0.44–1.68)</td>
<td>.66</td>
<td></td>
</tr>
<tr>
<td>All patients transplanted (n = 437)§</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Engraftment or pp65 antigenemia</td>
<td>No</td>
<td>1.0 (—)</td>
<td>—</td>
<td>1.0 (—)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Engraftment</td>
<td>Yes</td>
<td>1.10 (0.74–1.64)</td>
<td>.63</td>
<td>0.14 (0.88–1.47)</td>
<td>.34</td>
<td></td>
</tr>
<tr>
<td>CMV disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Engraftment or pp65 antigenemia</td>
<td>No</td>
<td>1.0 (—)</td>
<td>—</td>
<td>1.0 (—)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Engraftment</td>
<td>Yes</td>
<td>0.32 (0.12–0.82)</td>
<td>.02</td>
<td>0.70 (0.41–1.17)</td>
<td>.17</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. RR, relative risk; CI, confidence interval.

* Controlled for underlying disease risk (low vs. intermediate vs. high), age (as continuous variable), donor type (matched related vs. mismatched related or unrelated), total body irradiation, CMV donor serostatus, transplant number, use of fluconazole prophylaxis.

† Patients were randomly assigned to 1 of 2 groups at engraftment.

‡ Unadjusted for any other factors due to relatively small no. of events; stepwise inclusion of each factor (total body irradiation, age, donor type, CMV donor serostatus) but did not qualitatively change unadjusted results.

§ Additional analysis to account for patients who died early, did not engraft, or were unable to receive ganciclovir at engraftment; group of patients who did not receive high-dose acyclovir includes patients who received ganciclovir either at time of engraftment or based on antigenemia.

the first 2 years after transplant when calculated for all patients transplanted (group 1, 7/112 [6.3%]; group 2, 14/114 [12.3%]; group 3, 8/133 [6.0%; P = .14) and for all patients with CMV disease (group 1, 7/18 [38.9%]; group 2, 14/24 [58.3%]; group 3, 8/17 [47.1%]; P = .45).

Discussion

This study suggests that high-dose acyclovir given from day −5 until engraftment does not improve survival after allogeneic marrow transplant when ganciclovir is given at engraftment or for pp65 antigenemia. Furthermore, there is no evidence that high-dose acyclovir reduces CMV disease or CMV-related mortality.

In the present study, patients who had received high-dose acyclovir followed by ganciclovir at engraftment had no apparent survival benefit compared to patients who did not receive high-dose acyclovir and were given either ganciclovir at engraftment or for pp65 antigenemia. Although the retrospective nature of this study is a limitation, the 3 groups were remarkably well matched in terms of known risk factors for both CMV disease and transplant survival. Moreover, after controlling for factors associated with increased transplant mortality, there was no evidence of improved survival associated with high-dose acyclovir (table 1). Although low-dose acyclovir was given to patients who were HSV-seropositive before transplant, this is highly unlikely to confound the results of this study because acyclovir doses used for HSV prophylaxis have no effect on CMV disease or survival [2, 14]. While this study lacked sufficient power to detect any specific difference, the data do not suggest any survival benefit with high-dose acyclovir. Because the studies of high-dose acyclovir that showed a survival benefit included mainly good-risk patients (i.e., low incidence of severe acute GvHD, HLA-matched related donors, younger age), we tested the hypothesis that the effect of high-dose acyclovir may be restricted to these patients; however, there was no evidence that low-risk patients benefited more from high-dose acyclovir, although the number of such patients may be too small to make a firm conclusion.

This study also confirmed that ganciclovir given at engraftment is highly effective in preventing CMV disease during the first 100 days after allogeneic marrow transplant. Breakthrough CMV disease in patients who received ganciclovir virtually did not occur. However, late-onset CMV disease was
Figure 1. Kaplan-Meier estimate of survival in engrafted patients (A, primary analysis) and in all patients transplanted during study period (B), including patients who died early or did not meet criteria to start ganciclovir (GCV) treatment. $P$ not significant for all comparisons.

ACV, acyclovir.

common in patients who received ganciclovir at engraftment. In contrast, intermittent CMV pp65 antigenemia–guided early treatment in which ganciclovir is initiated when $\geq 3$ positive cells are detected in two slides and discontinued when antigenemia becomes negative is associated with more early CMV disease [13]. We reported earlier that the higher incidence of CMV disease in patients who received intermittent pp65 antigenemia–guided ganciclovir was due to a lack of treatment of low-grade antigenemia and early discontinuation of ganciclovir based on a negative test [13]. Nevertheless, the higher incidence of early CMV disease with that strategy did not lead to a higher mortality rate due to less invasive fungal infections and less late CMV disease [13].

In conclusion, there appears to be no evidence that high-dose acyclovir given for CMV prophylaxis adds benefit when ganciclovir is given at engraftment or for pp65 antigenemia. Thus, additional treatment of high-dose acyclovir during the early posttransplant period may not be required if ganciclovir is given at engraftment or based on pp65 antigenemia or detection of CMV DNA by PCR.
Acknowledgments

We thank Terri Cunningham, Terry Stevens-Ayers, and Patricia Wooger for data collection and Jennifer Shotwell for manuscript preparation.

References