Cytomegalovirus Infection After Autologous Bone Marrow Transplantation With Comparison to Infection After Allogeneic Bone Marrow Transplantation

By John R. Wingard, Donald Yen-Hung Chen, William H. Burns, Donald J. Fuller, Hayden G. Braine, Andrew M. Yeager, Herbert Kaiser, Philip J. Burke, Michael L. Graham, George W. Santos, and Rein Saral

Cytomegalovirus (CMV) infection was detected in 65 of 143 (45%) autologous bone marrow transplant (BMT) patients. CMV pneumonitis occurred in only 2% of the patients and CMV retinitis occurred in none. Infection occurred in half of the 40 initially seronegative patients and 47% of the 94 initially seropositive patients. Among initially seropositive patients, platelet recovery was slower in infected patients than in those not infected (97 v 35 days median, P = .003), and neutrophil recovery was slightly delayed in infected patients (31 days v 24 days, P = .02).

Although the incidence of CMV infection was comparable in autologous and allogeneic BMT patients, CMV pneumonitis was less frequent in autologous BMT patients (2% v 12%, P < .001). The risk for CMV pneumonitis in autologous BMT patients was comparable with that in allogeneic BMT patients without graft-vs-host disease (GVHD) (2% v 6%), but significantly lower than the risk in allogeneic BMT patients with GVHD (2% v 23%, P < .001).

From the Oncology Center, The Johns Hopkins Medical Institutions, Baltimore, MD.

Supported in part by National Institutes of Health Grants No. CA06973, CA15396, and CA40282.

Presented, in part, at the Third International Autologous Bone Marrow Transplantation Symposium, Houston, December 5, 1986.

Address reprint requests to John R. Wingard, MD, Johns Hopkins Oncology Center, Room 3-121, 600 N Wolfe St, Baltimore, MD 21205.

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

© 1988 by Grune & Stratton, Inc.

© 1988 by Grune & Stratton, Inc.
0006-4971/88/7105-00343.00/0

Differences were tested by Fisher's exact test or chi square test as calculated by Epistat, a computer software program. Time to platelet recovery was calculated by Kaplan-Meier plots and analyzed by the log-rank and generalized Wilcoxon tests, as calculated by Survapak-PC, a computer software program. Patients were advised of the risks of marrow transplantation and the attendant procedures and gave informed consent in accordance with the guidelines of the Joint Committee of Clinical Investigation of The Johns Hopkins Hospital and The Johns Hopkins University School of Medicine.

RESULTS

Patient characteristics The autologous BMT patients' characteristics are listed in Table 1. The patients were treated between November 1976 and October 1985. One hundred forty-three patients were studied. One hundred twenty-seven were alive 25 days after BMT. 117 patients were alive at day 50, 101 at day 100, and 90 survived 150 days or greater.

Incidence of CMV infection. Evidence for CMV infection was detected in 65 patients (45%). CMV was recovered from one or more specimens in 27 patients (19%). The actuarial incidence of virus excretion during the first 50 days after BMT was 18% (Fig 1): 6% in seronegative patients and 28% in seropositive patients (P < .01 by the log-rank and Wilcoxon tests). Seven patients (5%) had CMV viremia. The median onset of CMV excretion and viremia was 14 and 49 days, respectively. None of the patients developed CMV pneumonitis. Three (2%) developed CMV pneumonitis at 15, 38, and 38 days after BMT. CMV pneumonitis was fatal in all three patients.

Pretransplant CMV serology was assayed in 134 patients. Ninety-four (70%) were seropositive before transplant. Forty were seronegative and sera were not tested in nine patients.

Table 1. Characteristics of 143 Autologous BMT Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, in years (range)</td>
<td>21 (3-58)</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>84/59</td>
</tr>
<tr>
<td>Diagnoses</td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>35</td>
</tr>
<tr>
<td>ALL</td>
<td>50</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>33</td>
</tr>
<tr>
<td>Solid tumor</td>
<td>17</td>
</tr>
<tr>
<td>CML</td>
<td>8</td>
</tr>
<tr>
<td>Conditioning regimen</td>
<td></td>
</tr>
<tr>
<td>Cy/TBI/Adria</td>
<td>12</td>
</tr>
<tr>
<td>Cy/TBI/Adria/V</td>
<td>3</td>
</tr>
<tr>
<td>Cy/LPAM</td>
<td>1</td>
</tr>
<tr>
<td>Cy/TBI</td>
<td>76</td>
</tr>
<tr>
<td>Bu/Cy</td>
<td>51</td>
</tr>
<tr>
<td>Pretransplant CMV serology</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>94</td>
</tr>
<tr>
<td>Negative</td>
<td>40</td>
</tr>
<tr>
<td>Use of granocyte transfusions</td>
<td>16</td>
</tr>
<tr>
<td>Ex vivo marrow treatment</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>17</td>
</tr>
<tr>
<td>Monoclonal anti-T cell antibody</td>
<td>12</td>
</tr>
<tr>
<td>4-hydroperoxy cyclophosphamide</td>
<td>114</td>
</tr>
</tbody>
</table>

Abbreviations: AML, acute myelogenous leukemia; ALL, acute lymphocytic leukemia; CML, chronic myelogenous leukemia; Cy, cyclophosphamide; TBI, total body irradiation; Adria, Adriamycin; V, vincristine; LPAM, melphalan; Bu, busulfan.

The actuarial incidence of CMV excretion during the first 50 days after autologous BMT in 143 patients was 6% among seronegative patients and 28% among seropositive patients (P < .01).

The incidence of overall infection among seronegative patients was 50% (20 of 40) (Table 2). Of the 36 seronegative patients with follow-up serologic tests 18 seroconverted (50%) at a median time of 24.5 days (10 to 49). Peak anti-CMV antibody titers equaled or exceeded 1:128 in seven, 1:64 in six, 1:32 in three, and 1:16 in two. Only two of the 40 seronegative patients (5%) excreted CMV at 27 and 49 days; neither seroconverted. Neither excretor developed significant clinical manifestations of infection even though one became viremic 49 days after BMT. Four seronegative patients were recipients of granulocyte transfusions; none seroconverted.

To examine the possibility that antibody passively conferred by transfusion of blood products might give false serologic evidence of active infection, we examined changes in antibody to other herpesviruses highly prevalent in the normal adult blood donor population. We reasoned that antibodies to these other viruses would also be transferred if passive transfer were the explanation for the anti-CMV serologic response. Of the 13 patients with peak anti-CMV titers of 1:64 or greater, five had concomitant testing of antibodies against varicella-zoster (VZV) and herpes simplex (HSV) no change in antibody titers against these other
viruses occurred at the time that anti-CMV antibody developed. Of the three with peak anti-CMV titers of 1:32, two had concomitant anti-VZV and HSV testing with no change. One of the two patients with peak anti-CMV titer of 1:16 had concomitant testing of anti-Epstein-Barr Virus (EBV) serology with no change in EBV serology as the anti-CMV antibody appeared, while the other patient seroconverted on day 39, after cessation of transfusions.

The incidence of total infection among seropositive patients was 47% (44 of 94). Twenty-four (26%) excreted CMV with onset occurring as early as pretransplant (in eight patients) and as late as 78 days after BMT. Six (6%) became CMV viremic (with onset between 21 and 151 days after BMT). Two patients developed CMV pneumonitis. Twenty-seven of the seropositive patients (33% of those with follow-up sera tested) experienced a fourfold rise in antibody titer. Seven of these excreted virus, two became viremic, and one developed CMV pneumonitis. Twenty-seven of the seropositive patients (33% of those with follow-up sera tested) experienced a fourfold rise in antibody titer. Seven of these excreted virus, two became viremic, and one developed CMV pneumonitis. Fifty-four patients did not have a fourfold rise in CMV antibody titer. Seventeen of these developed positive cultures, four became viremic, and one developed CMV pneumonitis. Thus, seroconversion did not correlate well with CMV excretion or severe CMV disease. Thirteen of the seropositive patients did not have follow-up titers 2 weeks or more posttransplant. None of these excreted virus, became viremic, or developed CMV pneumonitis.

CMV antibody status before transplant was unknown in nine patients. One of these nine excreted CMV and developed CMV pneumonitis.

Rate of platelet recovery. Because an earlier report suggested that CMV infection delayed platelet recovery among autologous BMT patients, we examined the time required for platelet recovery. We separated patients into those initially seronegative and those initially seropositive to determine the relative effects of primary and non-primary infection. Since platelet recovery did not occur in all patients at the time of last measurement or death or leukemic relapse ensued before platelet recovery, a Kaplan-Meier time-to-event analysis was performed.

Platelet recovery by 150 days occurred in 87% of seronegative patients without CMV infection but in only 57% of patients with CMV excretion or seroconversion. The median time to platelet recovery was 41 days (95% confidence interval [CI], 34, 73) for patients without and 48 days (95% CI, 33, infinity) for patients with infection. This difference was not significant by the log-rank or Wilcoxon test (P = .10).

In seropositive patients, platelet recovery was calculated comparing patients with or without virus excretion, seroconversion, or total infection (Table 3). Platelet recovery at 150 days occurred in 81% of patients without infection and 62% of patients with CMV infection. The median time to platelet recovery was 35 days (95% CI, 30, 70) and 97 days (95% CI, 50, 191), respectively (P = .01 by the log-rank test and P = .003 by the generalized Wilcoxon test) (Fig 2).

Rate of neutrophil recovery. Neutrophil recovery was assessed separately in initially seropositive and seronegative patients. Among initially seronegative patients, those with CMV infection had neutrophil recovery at a median of 29 days (95% CI, 21, 35), uninfected patients recovered at a median of 24 days (95% CI, 19, 31), respectively (P = .10 by Wilcoxon and log-rank tests). CMV-infected seropositive patients had a slightly slower neutrophil recovery (median of 31 days, 95% CI of 27, 35) than noninfected patients (median of 24 days, 95% CI of 21, 35).

![Fig 2. Effect of non-primary CMV infection on platelet recovery. Initially seropositive patients with CMV infection recovered platelet function (untransfused count of 50,000/ml or greater) at a median of 97 days after BMT compared with 35 days for noninfected patients (P = .003).](https://www.bloodjournal.org)
patients with CMV infection in allogeneic BMT patients. Seroconversion occurred in 49 of the 106 (46%) BMT patients were routinely followed-up for a minimum of only 50 days posttransplant in contrast to 37/143 (26%) of the seronegative allogeneic BMT patients. Sixty-seven percent of the allogeneic regimens were the same.

Pretransplant CMV antibody status was assayed in 347 of the autologous BMT patients. Sixty-seven percent of autologous BMT patients tested were seropositive before BMT compared with 70% of tested autologous BMT patients. Seroconversion occurred in 49 of the 106 (46%) seronegative autologous BMT patients who had sera tested 2 weeks or more after BMT (compared with 50% of the seronegative autologous BMT patients as indicated above).

Because of fewer postengraftment complications, autologous BMT patients were routinely followed-up in our clinic for a minimum of only 50 days posttransplant in contrast to 100 days for allogeneic BMT patients. Since this shorter follow-up period could have resulted in fewer infections being detected in the autologous BMT recipients, the two groups were re-analyzed considering only infections detected during the first 50 days after transplant. There were no differences in rates of virus excretion or viremia between autologous and allogeneic BMT patients during the first 50 days. Seropositive autologous BMT patients had a comparable excretion rate to seropositive allogeneic BMT patients and seronegative autologous BMT patients also had an equivalent excretion rate to seronegative allogeneic BMT patients. The seroconversion rate in allogeneic BMT patients was half that of the autologous BMT patients during the first 50 days, but both groups had equivalent seroconversion rates overall. Despite similar primary and non-primary infection rates in the two transplant groups, there was a significantly greater risk for CMV pneumonitis after allogeneic BMT (12% v 2%, \(P = .0002\)) (Table 4).

The CMV excretion rate among allogeneic BMT patients was not affected by acute GVHD. The actuarial incidence of CMV excretion at 1 year was 36% in patients without GVHD and 41% in those with acute GVHD (\(P = .44\) by the log-rank test and \(P = .74\) by the Wilcoxon test). Figure 4 demonstrates that the actuarial incidence of CMV pneumonitis in allogeneic BMT patients with acute GVHD (23%) was greater than either the incidence of CMV pneumonitis in those without acute GVHD (6%) (\(P < .001\) by the log-rank test and \(P < .002\) by the Wilcoxon test) or the incidence of CMV pneumonitis in autologous BMT patients (2%) (\(P < .001\) by the log-rank and Wilcoxon tests). The incidence of CMV pneumonitis after allogeneic BMT in the absence of acute GVHD was not statistically greater than the risk of CMV pneumonitis after autologous BMT.

**DISCUSSION**

CMV has historically been the most common infectious cause of death in allogeneic BMT patients.\(^6,11\) As shown in this study, in contrast to allogeneic BMT, the risk for life-threatening CMV infection after autologous BMT is low.

The reasons for this do not appear to be related to different rates of infection. Approximately two thirds of the patients receiving both types of transplants were seropositive before transplant and thus had latent endogenous virus. Approximately half of the initially seronegative patients receiving both types of transplants seroconverted. Thus, primary infection rates were comparable. Among seropositive patients non-primary infection rates were also comparable in the two

**Table 4. Comparison of CMV Infection Between Autologous and Allogeneic BMT Patients**

<table>
<thead>
<tr>
<th>CMV Occurrence</th>
<th>Type of Transplant [No. Positive/Total Patients (%)]</th>
<th>Difference (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV excretion</td>
<td>27/143 (19%)</td>
<td>119/386 (31%)</td>
</tr>
<tr>
<td>During first 50 days</td>
<td>23/143 (16%)</td>
<td>58/386 (15%)</td>
</tr>
<tr>
<td>Seroconversion</td>
<td>45/134 (34%)</td>
<td>116/347 (33%)</td>
</tr>
<tr>
<td>During first 50 days</td>
<td>37/134 (28%)</td>
<td>49/347 (14%)</td>
</tr>
<tr>
<td>Total infection</td>
<td>65/143 (45%)</td>
<td>181/386 (47%)</td>
</tr>
<tr>
<td>During first 50 days</td>
<td>59/143 (41%)</td>
<td>100/386 (26%)</td>
</tr>
<tr>
<td>Retinitis</td>
<td>0/143 (0%)</td>
<td>1/386 (0.3%)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>3/143 (2%)</td>
<td>45/386 (12%)</td>
</tr>
</tbody>
</table>

Fig 3. Effect of non-primary CMV infection on neutrophil recovery. Initially seropositive patients with CMV infection recovered neutrophil function (count of 500 cells/μL or greater) at a median of 31 days after BMT compared with 24 days for noninfected patients (\(P = .02\)).
transplant groups. During the first 50 days after transplant, equivalent proportions of patients excreted CMV from any site and developed positive cultures and became viremic. Allogeneic BMT patients appeared to mount humoral responses to CMV slower than autologous BMT patients (as manifested by a lower seroconversion rate at day 50), but they had a comparable seroconversion rate overall. The occurrence of acute GVHD did not increase the rate of virus excretion after allogeneic BMT. The total infection rates were equivalent in the two transplant groups and are comparable to the experience reported in other allogeneic BMT patients.9,15

Allogeneic BMT patients with acute GVHD had a higher rate of CMV pneumonitis than either allogeneic BMT patients without acute GVHD or autologous BMT patients. With comparable infection rates between autologous and allogeneic BMT patients and comparable virus excretion rates between allogeneic BMT patients with or without GVHD, GVHD appeared to have affected the outcome of infection rather than its occurrence. The patient's ability to mount CMV-specific cytotoxic immune responses has been shown to be an important determinant of outcome.10 Thus, GVHD could have reduced the patient's ability to control the infection by reducing his immune competence11 either by the disease itself or the immunosuppression employed to treat or prevent it. Altered immunopathologic events have also been proposed to explain the development of CMV pneumonia.22 Further study is needed to clarify the factors associated with GVHD that affect the outcome of CMV infection.

Since life-threatening CMV disease was uncommon after autologous BMT, strategies to reduce CMV pneumonitis being used in allogeneic BMT patients, such as prophylactic intravenous (IV) CMV immunoglobulin13-15 or the provision of CMV seronegative blood products16 do not, at this time, seem appropriate as routine therapy for this patient population.

An earlier study in autologous BMT patients20 suggested that CMV infection affected the rate of platelet recovery (perhaps by infection of megakaryocytes) and that prevention of CMV infection through the use of seronegative blood products would speed platelet recovery and reduce the reliance on platelet transfusions. Because that study was uncontrolled, the numbers were small, and the groups compared were seronegative v seropositive patients, and thus differences between primary and non-primary infection were not considered, conclusions must be tentative. Differences between primary and non-primary infection are likely to be important since in allogeneic BMT patients prior CMV infection resulting in pretransplant seropositivity confers a greater risk for CMV pneumonitis.18,27,28

In this report, we compared the effects of primary and non-primary CMV infection separately. Although there was a slightly longer time to platelet recovery and ultimately fewer patients with primary infection achieved platelet recovery during the first 150 days, these differences were not statistically significant. Since the number of initially seronegative patients was small (40), a larger sample size must be studied to demonstrate whether primary CMV infection delays platelet recovery. However, among seropositive patients, those with CMV infection had significantly slower platelet recovery. Clearly, controlled trials are required to address definitively how important CMV infection is in the rate of platelet recovery and whether the provision of CMV seronegative blood products to initially seropositive patients can speed platelet recovery and reduce the reliance on platelet transfusions.

It is of interest that despite high rates of CMV infection in these BMT patients, CMV retinitis was a rare event occurring in only one patient who received an allogeneic BMT.19 This is in contrast to the experience in patients with the acquired immune deficiency syndrome where there is also a high rate of CMV infection and a high rate of CMV retinitis. There appears to be a difference in the character of the immunodeficiency in the two patient populations making one group more susceptible to lethal CMV pneumonitis and the other more susceptible to progressive retinitis.

In conclusion, although infection rates were similar between autograft and allograft recipients, CMV disease was less in autograft recipients. The low incidence of CMV pneumonitis found in this study is similar to the observations in syngeneic BMT patients (no cases in 100 patients)29 and autologous BMT patients (three cases in 70 patients),30 despite similar rates of infection to allogeneic BMT patients.9 The rate of CMV pneumonitis in autologous and allogeneic BMT patients without acute GVHD were comparable, and considerably less than the incidence in allogeneic BMT patients with GVHD. However, non-primary CMV infection appeared to have an impact on hematologic reconstitution after autologous BMT, especially platelet recovery. Further study is needed to determine the impact of primary CMV infection on hematologic reconstitution.

ACKNOWLEDGMENT

We gratefully acknowledge the secretarial assistance of Sandal L. Beggs.
REFERENCES


Cytomegalovirus infection after autologous bone marrow transplantation
with comparison to infection after allogeneic bone marrow transplantation

JR Wingard, DY Chen, WH Burns, DJ Fuller, HG Braine, AM Yeager, H Kaiser, PJ Burke, ML Graham
and GW Santos

Updated information and services can be found at:
http://www.bloodjournal.org/content/71/5/1432.full.html

Articles on similar topics can be found in the following Blood collections

Information about reproducing this article in parts or in its entirety may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests

Information about ordering reprints may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#reprints

Information about subscriptions and ASH membership may be found online at:
http://www.bloodjournal.org/site/subscriptions/index.xhtml