Cytomegalovirus Infection Causes Delayed Platelet Recovery After Bone Marrow Transplantation

By Leo F. Verdonck, Gijsbert C. de Gast, Hans G. van Haegten, H. Karel Nieuwenhuis, and Adriaan W. Dekker

The pathogenic effect of cytomegalovirus (CMV) infection on the hematopoietic recovery after bone marrow transplantation (BMT) was retrospectively studied in 87 recipients of (nonpurged) autologous BMT and in 56 recipients of allogeneic BMT from HLA-identical siblings. Indications for allogeneic BMT were lymphomas or acute leukemias and for allogeneic BMT various malignancies or aplastic anemia. Patients were divided for the study in two groups, CMV-positive and CMV-negative on the basis of the CMV status pretransplant, and CMV-negative patients were kept CMV-negative by the local transfusion policy. In allogeneic BMT recipients, platelet recovery was significantly slower in CMV-positive patients than in CMV-negative patients (platelets > 50,000 cells/μL after 41 days v 27 days, P = .007). This difference held true when patients with acute graft-versus-host disease above grade I were excluded (platelets > 50,000 cells/μL after 42 days v 24 days, P = .01). In autologous BMT, the negative effect on platelet recovery was present in patients with lymphomas, but absent in patients with acute leukemias. Patients with acute leukemias had a very delayed recovery of platelets and granulocytes after autologous BMT, irrespective of the CMV status, probably due to the original stem cell disorder. Platelet recovery was significantly slower in CMV-positive autologous BMT recipients with lymphomas than in those not infected (platelets > 50,000 cells/μL after 36 days v 24 days, P = .0002). The presence of CMV infection had no effect on the recovery of granulocytes in autologous or allogeneic BMT. These data show that CMV infection causes delayed platelet recovery after BMT; however, in autologous BMT, the underlying disease (ie, acute leukemia) is more determinant for hematopoiesis after BMT.

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CMV INFECTION DELAYS PLATELET RECOVERY AFTER BMT

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Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Underlying disease</th>
<th>CMV-Negative</th>
<th>CMV-Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML</td>
<td>31/12</td>
<td>24/20</td>
</tr>
<tr>
<td>ALL</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>NHL</td>
<td>26</td>
<td>16</td>
</tr>
<tr>
<td>HD</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Median no. of nucleated cells (×10^6/kg) in cryopreserved graft (range)</td>
<td>1.5 (0.6-2.5)</td>
<td>1.6 (0.5-4.1)</td>
</tr>
<tr>
<td>CFU-GM (×10^3/kg)</td>
<td>6.1 (1.0-24.0)</td>
<td>7.3 (0.6-40.0)</td>
</tr>
<tr>
<td>BFU-E (×10^3/kg)</td>
<td>14.7 (2.9-26.0)</td>
<td>16.2 (1.8-21.6)</td>
</tr>
<tr>
<td>Male/female</td>
<td>31/12</td>
<td>24/20</td>
</tr>
<tr>
<td>Median age, y (range)</td>
<td>30 (14-58)</td>
<td>38 (15-60)</td>
</tr>
<tr>
<td>Median no. of nucleated cells (×10^6/kg) in graft (range)</td>
<td>0.07 (0.02-0.26)</td>
<td>0.07 (0.02-0.18)</td>
</tr>
<tr>
<td>CFU-GM (×10^3/kg)</td>
<td>22.9 (1.7-64.0)</td>
<td>27.8 (3.7-70.0)</td>
</tr>
<tr>
<td>BFU-E (×10^3/kg)</td>
<td>8.6 (1.6-34.0)</td>
<td>11.6 (1.5-69.0)</td>
</tr>
<tr>
<td>Underlying disease</td>
<td>CMV-Positive</td>
<td>CMV-Negative</td>
</tr>
<tr>
<td>AML</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>ALL</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>CML</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Other malignancy*</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Median no. of nucleated cells (×10^6/kg) in graft (range)</td>
<td>0.07 (0.02-0.26)</td>
<td>0.07 (0.02-0.18)</td>
</tr>
<tr>
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<td>8.6 (1.6-34.0)</td>
<td>11.6 (1.5-69.0)</td>
</tr>
<tr>
<td>Male/female</td>
<td>20/12</td>
<td>12/12</td>
</tr>
<tr>
<td>Median age, y (range)</td>
<td>31 (17-46)</td>
<td>32 (14-48)</td>
</tr>
<tr>
<td>No. of recipients of allogeneic BMT</td>
<td>32</td>
<td>24</td>
</tr>
<tr>
<td>No. of recipients of autologous BMT</td>
<td>43</td>
<td>44</td>
</tr>
</tbody>
</table>


*Includes patients with multiple myeloma (4), metastatic melanoma (3), severe aplastic anemia (2), Hodgkin’s disease (1), myelodysplastic syndrome (2).

CMV cultures became positive in patients with IgG antibodies (latent infection). Because of the unequivocal results of CMV-seronegative patients with our transfusion policy: all CMV-seronegative patients developed acute graft-versus-host disease (GVHD) grade I or grade II; none of the patients developed greater than grade II acute GVHD. Twelve autologous BMT recipients developed grade II acute GVHD before they met the criteria for hematopoietic recovery.

CMV-negative patients, supported by the transfusion policy as outlined above, remained CMV-negative during the study period. None of the BMT recipients with latent CMV infection excreted CMV at the time of BMT. Twenty-one (of 24) autologous BMT recipients with latent infection were evaluable (alive ≥30 days posttransplant) for reactivation of CMV infection, and 19 of 21 (90%) had reactivation as demonstrated by CMV cultures. Virus excretion occurred after a median of 64 (range 30 to 83) days posttransplant. Forty (of 44) autologous BMT recipients with latent infection were evaluable for reactivation. Eight of 40 (20%) had reactivation by CMV cultures (five patients; virus excretion after a median of 60 [range 30 to 85] days with or without antibody increase) or by CMV serology (three patients; without CMV excretion). CMV-pneumonia developed in only 1 of 44 (2%) CMV-positive autologous BMT recipients, but in 6 of 22 (27%) CMV-positive autologous BMT recipients (including four patients with preceding acute GVHD). All patients with CMV pneumonia died, despite early treatment with the antiviral agent DHPG and/or CMV-Ig.

The reactivation of latent CMV infection before hematopoietic recovery (see below) was achieved occurred in 9 of 21 evaluable allotransplant recipients and in 4 of 37 evaluable autotransplant recipients.

Hematopoietic recovery in patients with lymphomas treated with autologous BMT. The recovery of granulocytes greater than 500 cells/μL occurred after a median number of 21 days (range, 11 to 33) in CMV-negative patients and after a median number of 24 days (range, 14 to 46) in CMV-positive patients. This difference was not significant. The recovery of platelets greater than 50,000 cells/μL occurred significantly faster in CMV-negative patients (Fig 1); the time to reach this platelet count occurred after a median number of 24 days (range, 13 to 34) in CMV-negative patients versus a median number of 36 days (range, 17 to 87) in CMV-positive patients ($P = .0002$).

RESULTS

Patient characteristics and CMV-virology. The clinical characteristics for CMV-negative and CMV-positive patients are summarized in Table 1. Median age of CMV-positive autologous BMT recipients was slightly higher; otherwise, characteristics were not different for both groups. Especially similar were the number of nucleated cells and committed stem cells in the graft, determined after cryopreservation and thawing for autologous marrow grafting and after in vitro T-cell depletion for allogeneic marrow grafting. After autologeneic BMT, 14 of 21 (67%) evaluable CMV-positive patients and 18 of 32 (56%) evaluable CMV-negative patients developed acute graft-versus-host disease (GVHD) grade I or grade II; none of the patients developed greater than grade II acute GVHD. Twelve autologous BMT recipients developed grade II acute GVHD before they met the criteria for hematopoietic recovery.

Fig 1. Recovery of platelets greater than 50,000 cells/μL after autologous BMT in CMV-negative and CMV-positive patients with lymphomas.
Hematopoietic recovery in patients with acute leukemias treated with autologous BMT: The recovery of granulocytes greater than 500 cells/µL occurred after a median number of 37 days (range, 12 to 45) in CMV-negative patients and after a median number of 27 days (range, 13 to 54) in CMV-positive patients. This difference was not significant. The recovery of platelets greater than 50,000 cells/µL occurred after a median number of 67 days (range, 18 to 132) in CMV-negative patients and after a median number of 51 days (range, 33 to 244) in CMV-positive patients. This difference was not significant. However, the number of patients is rather small (13 v 21) in this subgroup.

Furthermore, we analyzed separately patients with AML and patients with ALL in relation to their CMV status and, although the number of patients in each category became rather small, the hematopoietic recovery was not influenced by CMV infection in both diseases (data not shown). In analyzing the hematopoietic recovery for the disease, irrespective of CMV status, no significant differences were observed between patients with AML or with ALL (data not shown).

Hematopoietic recovery in patients treated with allogeneic BMT: The recovery of granulocytes greater than 500 cells/µL occurred after a median number of 22 days (range, 12 to 38) in CMV-negative patients and after a median number of 24 days (range, 16 to 40) in CMV-positive patients. This difference was not significant. The recovery of platelets greater than 50,000 cells/µL occurred significantly faster in CMV-negative patients (Fig 2), and the time to reach this platelet count occurred after a median number of 27 days (range, 15 to 165) in CMV-negative patients versus a median number of 41 days (range, 19 to 291) in CMV-positive patients (P = .007). To eliminate a (negative) GVHD effect on the hematopoietic recovery, we excluded in this analysis patients who developed acute GVHD grade II before they met the criteria for hematopoietic recovery. This happened in eight CMV-negative patients and in four CMV-positive patients. The recovery of granulocytes greater than 500 cells/µL was not significantly different in this subgroup (patients with no or grade I acute GVHD): 21 days (range, 12 to 33) in CMV-negative patients and 24 days (range, 19 to 40) in CMV-positive patients. However, the difference between CMV-negative and CMV-positive patients for the recovery of platelets remained (P = .01): platelets greater than 50,000 cells/µL occurred after a median number of 24 days (range, 15 to 165) in CMV-negative patients and after a median number of 42 days (range, 21 to 291) in CMV-positive patients (Fig 3).

**DISCUSSION**

This study indicates that CMV infection causes delayed platelet recovery after autologous and allogeneic marrow transplantation. The effect of CMV infection on platelet recovery is present in autologous BMT for patients with lymphomas, but not for patients with acute leukemias, and in allogeneic BMT CMV affects all patients. CMV infection has no effect on the recovery of granulocytes in autologous or in allogeneic BMT. Autologous BMT recipients with acute leukemias have a much slower recovery of granulocytes and platelets than autologous BMT recipients with lymphomas (and with CMV infection).

We have previously reported that CMV infection causes delayed platelet recovery after autologous BMT, but the number of patients was small and patients with lymphomas and with acute leukemias could not be analyzed separately.

In patients with acute leukemias, delayed platelet recovery and, to a lesser extent, also granulocytic recovery, has been reported after autologous (nonpurged) BMT. These data are confirmed in this study, and in addition we show that the hematopoietic recovery is not affected by CMV infection. The reason for the extreme delayed hematopoietic recovery after autologous BMT for patients with acute leukemias is unknown at the moment, but can probably be ascribed to the original stem cell disorder, continuing in remission.

The negative effect of CMV infection on the platelet recovery was pronounced in allogeneic BMT recipients. All allograft recipients received T-cell–depleted marrow grafts and CMV-positive and CMV-negative patients had similar numbers of nucleated marrow cells and committed stem cells in the graft. Because acute GVHD can cause prolonged pancytopenia, especially isolated thrombocytopenia after BMT, we excluded in our analysis patients who developed acute GVHD beyond grade I before they met the criteria for hematopoietic recovery after BMT. The negative impact of CMV infection on the recovery of platelets held true in this analysis.
Our observation that CMV infection causes delayed platelet recovery after autologous BMT was confirmed by Wingard et al., although confined to CMV-positive patients with reactivation of CMV infection. However, a very recent report by Reuss et al. could not demonstrate any effect of CMV infection, including CMV reactivation, on the recovery of platelets after autologous BMT. A major drawback of both studies was that blood products used for transfusion support were not screened for CMV status. This drawback was reflected by the fact that a high proportion of initially CMV-negative patients became CMV-positive (50%, and 23%, respectively). Thus, the conclusion drawn by Reuss et al., that CMV infection is not associated with delayed platelet recovery, is questionable. Furthermore, the majority of the autologous BMT recipients in both studies had acute leukemias. Because a delayed platelet recovery after autologous BMT is ubiquitous in these patients, the negative effect of CMV infection is probably camouflaged. The observed association between reactivation of CMV infection and delayed platelet recovery was not applicable in our study because almost all autologous BMT recipients achieved hematopoietic recovery before CMV reactivation occurred. Obviously, latent CMV infection itself is responsible for delayed platelet recovery in the early phase posttransplant.

The importance of a deliberate transfusion policy that effectively prevents CMV transmission to CMV-negative recipients was reported previously by our group and confirmed later in a large study. In the present study, none of the CMV-negative autologous or allogeneic BMT recipients acquired a (primary) CMV infection (and risk for CMV pneumonia) during the first 6 months after BMT. Although CMV pneumonia occurred in only 1 of 44 (2%) CMV-positive autologous BMT recipients and in 6 of 22 (27%) CMV-positive allogeneic BMT recipients, the risk of CMV pneumonia in autologous BMT is not negligible, as was demonstrated by Reuss et al., who observed an incidence of about 10%.

The mechanisms by which CMV infection causes a delay in platelet recovery are gradually being elucidated: CMV infection can be directly cytotoxic for megakaryocytes or their progenitors and also to hematopoietic stem cells in the mouse model, and pursuing to human studies in vitro, the marrow progenitor cell can be infected by CMV and disturb hematopoiesis; indirect impairment of hematopoiesis is also possible through infection of marrow stromal cells, including perturbation of growth factor production.

In conclusion, CMV infection causes delayed platelet recovery after BMT. However, in autologous BMT the underlying disease is more determinant for hematopoiesis after transplantation. The delayed platelet recovery requires more transfusions. A transfusion policy that prevents transmission of CMV to CMV-negative BMT recipients will have a major impact on morbidity and mortality and on expenses of treatment.

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Cytomegalovirus infection causes delayed platelet recovery after bone marrow transplantation

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