Cytomegalovirus Infection After Bone Marrow Transplantation: An Association With Acute Graft-v-Host Disease

By Wesley Miller, Patrick Flynn, Jeffrey McCullough, Henry H. Balfour, Jr, Anne Goldman, Robert Haake, Philip McGlave, Norma Ramsay, and John Kersey

Among 181 patients undergoing allogeneic bone marrow transplantation over a five-year period (1978 through 1982), cytomegalovirus (CMV) infection was a frequent and often lethal complication. Recipient pretransplant serology was the most important predictor of posttransplant CMV infection. CMV infection occurred in 26/137 seronegative recipients and in 28/44 seropositive recipients (P < .001). Among patients who developed CMV infection, the time to infection was identical in seronegative and seropositive patients (median, 71 days post transplant). Bone marrow donor CMV serology did not significantly influence CMV infection rate. CMV infection was strongly associated with acute graft-v-host disease (AGVHD), occurring in 34/81 patients with AGVHD and 20/100 without GVHD (P < .001). AGVHD preceded CMV infection by 33.7 days (mean) in patients developing both complications. Patients who developed CMV infections had also received more cellular blood products post transplant. These data suggest that CMV infection may occur through reactivation of latent virus (in seropositive recipients) or through exogenous exposure, possibly through transfused blood products, but that duration of immunoincompetence may be more critical than route of exposure in timing of clinically evident CMV infection. Prophylaxis tailored to the likely infectious source and more effective GVHD prevention both may be critical in preventing CMV infection after bone marrow transplantation.

BONE MARROW TRANSPLANTATION is increasingly successful in the treatment of a variety of hematologic and immunologic disorders. Although transplantation is effective in restoring hematopoiesis, the early complications of graft-v-host disease (GVHD) and infection (especially viral) limit the success of this treatment modality. Cytomegalovirus (CMV) infection has been documented in 40% to 50% of patients undergoing marrow transplantation, with adults developing CMV infection more frequently than pediatric patients.1 In addition, interstitial pneumonitis, a severe and often fatal complication, is commonly associated with CMV infections.

In bone marrow transplantation, immunosuppression is multifactorial. Immunoinsufficiency may result from the patient’s primary disease, from the preparative regimen, from GVHD, or from treatment of GVHD. Several sources of CMV infection must also be considered. Immunosuppression may allow reactivation of latent virus in CMV seropositive patients. CMV might be transmitted with transplanted marrow from a seropositive donor. Finally, the multiple blood products that most patients receive in the early posttransplantation period may contain infective CMV particles. In an attempt to clarify the relative importance of these causes of immunosuppression and sources of infection, we analyzed the University of Minnesota experience with CMV in bone marrow transplantation over a five-year period.

METHODS AND MATERIALS

Patients. During a five-year period (1978 through 1982), 206 patients underwent allogeneic bone marrow transplantation at the University of Minnesota Hospitals. Of these patients, 13 were eliminated from analysis because they were secreting CMV before transplantation and 12 patients were eliminated because of inadequate data regarding donor CMV serology. Thus 181 patients were retrospectively analyzed for their entire posttransplant course. Both adult and pediatric patients were included. Patients were grouped according to CMV serology before transplantation and by age (younger than 16 years or 16 years or older). Forty-one recipients and 30 donors were judged seroreactive on the basis of positive complement fixation titers, while three recipients and three donors were judged seronegative on the basis of positive immunofluorescence titers (with negative complement fixation). Blood, urine, and throat cultures for CMV were obtained and serum titers determined for each patient weekly during hospitalization and again at posttransplant day 100. Complement fixation titers were done on all samples, although not all negative complement fixation titers were retested by immunofluorescence. At day 100, both complement fixation and immunofluorescence titers were determined for all patients. Additional cultures were obtained as clinically indicated. Prospectively collected data regarding patient age, disease, conditioning regimen, GVHD, CMV infection, and survival were available from the University of Minnesota Bone Marrow Transplant Database Management under the direction of Dr Anne Goldman.

Definitions. Seropositivity for CMV was defined by a complement fixation titer of $\geq 1:8$ or an immunofluorescence titer of $\geq 1:40$. Seropositivity was interpreted as indicating prior exposure, not active infection. All CMV infections were diagnosed on the basis of positive CMV culture from any site, tissue biopsy showing typical CMV inclusions, or a fourfold increase in titer of antibody against CMV. Our methods for culturing CMV and performing humoral titers were as previously described.

GVHD was diagnosed on the basis of clinical findings (rash, diarrhea, abdominal pain, hematemysal, jaundice, elevated liver enzymes), coupled with histologic changes of GVHD in biopsies of skin, liver, or gastrointestinal tract (stomach, duodenum, colon), using standard criteria. Any patient with at least grade 1 GVHD was considered to have GVHD.

Blood product usage. We evaluated the number of cellular blood products administered to each patient included in the study. For each patient, red blood cell units, platelet donor units, and granulocyte donor units were enumerated. Pediatric patients

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received smaller packed red cell units (125 mL) than did adult patients (approximately 300 mL), but platelet units were the same size for pediatric and adult patients. Cellular blood products were enumerated for each patient during the first 35 days after transplantation. Because the usual onset of detectable CMV infection is at post-bone marrow transplant day 50 to 55,\(^1\) it is likely that virus transmission or reactivation occurs during the early posttransplant period. In addition, CMV infection may increase transfusion requirements, and analysis of blood product requirements for the entire posttransplant course might not accurately reflect differences in blood product usage before CMV infection. We, therefore, evaluated blood product transfusion for each patient before the usual onset of CMV infection. (Complete transfusion data were not available for five patients. All five patients were seronegative, and only one developed CMV infection: a 14-year-old female, who died at posttransplant day 238 of relapsed acute lymphocytic leukemia (ALL). Of the remaining four, a 27-year-old male died at day +174 of relapsed chronic myelogenous leukemia (CML). The others remain alive without disease.)

Statistics. CMV incidence curves were estimated by the Kaplan-Meier product limit method similar to survival analysis, except that all patients were considered at risk for CMV until censoring at the time of death. The cumulative event proportions at one year were compared by \(t\) tests. Some factors that significantly affected CMV infection rates were also associated with one another (eg, age and GVHD). To study these associations, Cox multivariate regression analysis was carried out, using proportional hazards methods\(^5\) for CMV incidence and for survival. For this purpose, we used the P2L program from BDMP Statistical Software, Inc (Los Angeles). GVHD occurs some time after transplant and was therefore treated as a time-dependent covariate in the Cox model.\(^6\) Differences in blood transfusion amounts (comparing number of units received by patients developing CMV infection with the number of units received by patients remaining CMV-free) were analyzed using the Mann-Whitney rank sum test.

Autopsy data. Autopsy reports were available for 50 patients included in this study group. Autopsy reports were reviewed for evidence of CMV infection and for distribution of CMV at autopsy. CMV was identified histologically by the presence of typical intracellular inclusions in tissue specimens.

RESULTS

CMV infections were documented in 29.8% of bone marrow transplant patients. CMV infection was diagnosed by positive cultures in 46 patients, compatible tissue morphology in two, and seroconversion in six patients. (Five of these patients were seronegative before transplant; the sixth patient had CMV titers of 1:16 by complement fixation and 1:20 by immunofluorescence before bone marrow transplantation that rose to 1:64 by immunofluorescence and 1:640 by complement fixation during the posttransplant course.) We evaluated several factors that might predict risk for development of CMV. The first of these, recipient and donor serology prior to bone marrow transplantation, are shown in Table 1. Among 137 seronegative patients, 26 (estimated infection rate, 22.8%) developed CMV infection, while 28/44 (estimated infection rate, 79.6%) of seropositive patients developed CMV infection during the posttransplant course \((P < .001)\). The titer of CMV antibody present pretransplant, on the other hand, did not appear to influence infection rate. Among seropositive recipients, those with CMV complement fixation titers of 1:8 to 1:16 developed CMV infection in 15/21 cases. Recipients with complement fixation titers of 1:32 to 1:512 developed CMV infection in 14/23 cases. Thus recipient seropositivity (but not titer) was strikingly important in predicting CMV infection. Severity of infection was not apparently influenced by pretransplant serology, however. Twenty-three patients (12 seronegative and 11 seropositive) developed clinically apparent disease, while 31 patients had subclinical infections. Bone marrow donor serology, in contrast to recipient serology, had no significant influence on posttransplant CMV infection (32.7% \(v\) 47.6%, \(t\) = 1.6, \(p = .12\) (Table 1).

We also analyzed the time to CMV infection for patients who actually became infected. The median time to diagnosis in patients developing CMV infection was 71 days post-bone marrow transplantation. Interestingly, neither recipient nor donor pretransplant serology appeared to influence the time to infection. Seropositive recipients and seronegative recipients had identical time curves (Kaplan-Meier) for acquisition of CMV infection, both with medians of 71 days. This analysis may be biased, since the 51 patients who died without CMV were not included in these particular calculations.

Patients developing CMV infections were somewhat older (mean age, 17.5 years) than patients remaining free of CMV (mean age, 13.9 years). Time to CMV infection was examined using the Cox regression method with age as a covariate. Increasing age was a significant predictor of time to CMV; each additional year of age was associated with a 1.032 proportional increase in the likelihood of CMV infection. The increased risk in adults appears to relate to the increasing incidence of seropositivity with increasing age. Seropositive recipients had a mean age of 21.1 years, whereas seronegative recipients had a mean age of 13.0 years. When seronegative patients were grouped by age, patients of less than 16 years of age (mean, 7.4 years) had an 18.8% incidence of CMV infection (16/85), while seronegative

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<th>Table 1. CMV Infection After Bone Marrow Transplantation: Relationship to Recipient/Donor Pretransplant CMV Serology</th>
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<tr>
<td>Recipient Serology</td>
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* \(t\) Test on cumulative proportion without event by donor serology is 1.56, \(p = .12\).
† \(t\) Test on cumulative proportion without event by recipient serology is 6.73, \(p = .001\).
patients of 16 years or older (mean age, 22.2 years) had a nearly identical 19.2% (10/52) incidence of CMV infection. With Cox regression, age did not independently predict CMV infection when recipient serology and GVHD were included as covariates (Table 2).

The conditioning regimens used in bone marrow transplantation are a source of variation among patients. We evaluated the relationship between conditioning regimens and CMV infection rate. Seronegative patients receiving total body irradiation (chiefly for malignancies) had a 23.3% (7/30) incidence of CMV infection (x^2 = 0.11, P = .74). Similarly, seropositive patients receiving total body irradiation had a 59.3% (16/27) incidence of CMV infection compared with 70.6% (12/17) for those receiving total lymphoid irradiation (x^2 = 0.19, P = .66). Four patients received chemotherapy without irradiation before transplantation, and none of these developed CMV infection.

The relationship between blood transfusions and CMV infections in our patients is shown in Table 3. Patients who remained CMV-free received 33.3 units of blood (median), while those who developed CMV infection received more, with a median of 46.5 units of blood during the first 35 days after transplantation (P = .08). We also analyzed red blood cell and platelet transfusions for each patient. CMV-infected patients received significantly more red cell units (6.1 units, median) than did uninfected patients (5.0 units, median) (Z = 1.96, P = .05). CMV-infected patients also received more platelets (37.0 units) than did uninfected patients (25.5 units), although this difference was not statistically significant (Z = 1.28, P = .12 by Mann-Whitney). The products administered were not tested for CMV antibody. However, the overall incidence of CMV seropositivity in our blood donor population is 30%.

The association between acute GVHD (AGVHD) and CMV infection is shown in Table 4. Among patients with no AGVHD, 20% had posttransplant CMV infections, while 42% of those with AGVHD developed CMV infections. A Cox proportional hazards regression analysis was performed in which AGVHD was included as a time-dependent covariate. In this analysis of time to CMV, patients were included in the no AGVHD group until the time of diagnosis of AGVHD; at that point patients were switched to the AGVHD group. Thus if CMV was evident before the diagnosis of AGVHD, the risk of CMV would be associated with no AGVHD; when AGVHD preceded CMV, the risk of CMV infection was associated with AGVHD. CMV infection was significantly more likely to occur among patients with AGVHD. The relative risk for those with AGVHD was 3.24 times that for those without AGVHD (P < .001). A similar regression analysis of time to CMV was conducted with chronic GVHD as a time-dependent covariate, but this analysis failed to show an association of CMV with chronic GVHD (relative risk of CMV = 1.63, P = .40). Among patients surviving longer than 100 days, chronic GVHD was diagnosed in 22/93 (23.7%) CMV-uninfected and 15/39 (40.5%) CMV-infected patients (x^2 = 2.3, P = .13).

To further clarify the relationship between AGVHD and CMV, we compared the time to CMV and time to AGVHD in 24 patients who developed both. Acute GVHD preceded diagnosis of CMV by a mean of 33.7 days in these patients (t = 4.17, P < .001). Because AGVHD preceded CMV infection in most patients, we next sought a relationship between treatment of AGVHD and CMV infection. Table 5 shows CMV infection incidence according to maximal GVHD therapy. Patients were treated with topical or moderate- or high-dose corticosteroids, depending on the distribution and severity of AGVHD. As can be seen, although AGVHD appeared to influence CMV infection rate, the dose or route of administration of GVHD therapy did not obviously affect CMV infection rate. Among seronegatives, the CMV infection rate was similar whether the patient received topical or moderate- or high-dose corticosteroids (x^2 = 0.44, P = .80). Similarly, seropositive patients with AGVHD had nearly identical CMV infection rates regardless of GVHD therapy (x^2 = .11, P = .74).

Because recipient CMV serology, GVHD, age, and CMV infection were all interrelated factors, their association was further analyzed using Cox regression analysis. This method allowed us to test the association between rate of CMV infection and each of the factors while controlling for the effects of each of the remaining factors (Table 2). Both recipient serology and AGVHD were confirmed as significantly and independently related to CMV infection (both P < .001). Age, when we controlled for the effects of serology and AGVHD, did not contribute significantly to CMV risk (P = .41).

We evaluated the effect of CMV infection on survival.
patients developing CMV infection, 23/54 (43.0%) are alive one to five years after transplant, while 69/127 (54.3%) patients not developing CMV infection remain alive. Such data may not, however, accurately reflect the effect of CMV on survival. We therefore performed a multivariate analysis of the influence of various factors on survival. Factors included age (<16 v 16 or older), disease category (malignancy v other), high- v low-risk disease (see later), presence or absence of CMV infection, and presence or absence of GVHD. Patients were considered high risk if they were transplanted with acute nonlymphocytic leukemia (ANLL) in second or greater remission or in relapse; acute lymphocytic leukemia (ALL) in third or greater remission or in relapse; CML in accelerated phase, blast crisis, or post-remission; CML in chronic phase; or aplastic anemia. Patients with Fanconi’s anemia was also included in the high-risk category. Patients were considered low risk if they were transplanted with ANLL in first remission; ALL in first or second remission; CML in chronic phase; or aplastic anemia. Using Cox regression analysis, we analyzed the independent effects of these factors on survival, using disease category, risk category, and age as baseline characteristics and including CMV and GVHD as time-dependent covariates, since they are not baseline characteristics. CMV infection was associated with decreased survival (relative risk 2.1, \( P = .005 \)), as was high-risk disease (relative risk 1.72, \( P = .03 \)). Age (relative risk 1.31), disease category (relative risk 1.13), and GVHD (relative risk 1.4) were not independent predictors of survival in this analysis. In a separate analysis of 101 leukemic patients, we compared the effects of diagnosis (ANLL \( v \) ALL \( v \) CML), age, risk, CMV infection, and GVHD. Diagnosis did not influence survival (relative risk 1.0), while CMV infection again showed a negative influence on survival (relative risk 2.4, \( P = .01 \)), as did high-risk disease (relative risk 2.0, \( P = .025 \)). This multivariate analysis clearly demonstrates that CMV infection was associated with an increased mortality and indicates that the overall risk of death among CMV-infected patients was 2.1 times that of those without CMV.

To further clarify the influence of CMV infection on mortality, we reviewed autopsy reports of 50 patients. Among 15 patients with autopsy evidence of CMV disease, 14 had interstitial pneumonitis. Only one patient had lung CMV without evidence of interstitial pneumonitis. There were an additional ten cases of interstitial pneumonitis not associated with CMV, so CMV was a candidate pathogen in 58.8% of cases of interstitial pneumonitis. The distribution of CMV in autopsy tissues included lung (15 cases), liver (six), stomach (five), colon (four), small bowel (three), esophagus (two), adrenal (two), skin (two), rectum (one), and kidney (one). Nineteen patients included in this autopsy series had antemortem culture or biopsy evidence of CMV infection, and 15 of those patients had CMV demonstrable at autopsy. Of 31 patients who did not have antemortem evidence of CMV infection, no patient had CMV at autopsy.

**DISCUSSION**

The data obtained in this study reveal or confirm several important points regarding CMV infection after bone marrow transplantation: CMV is an important source of post-transplant mortality, and seropositive recipients are not protected against severe infection. To the contrary, recipient (but not donor) seropositivity is an important predictor of posttransplant CMV infection. Red cell and platelet transfusions may be a source of CMV infection, possibly leading to infection in as many as 20% of patients, although the exact role of this infectious source was not clear in our studies. As previously observed,\(^7\) there appears to be an important relationship between AGVHD and CMV infection, although we failed to confirm the relationship between CMV and chronic GVHD reported by Lönnquist et al.\(^8\)

Seropositive patients developed CMV infections nearly three times as frequently as seronegative patients after bone marrow transplantation. This parallels the findings of Meyers et al\(^7\) that recipient (but not donor) seropositivity is strongly associated with CMV pneumonitis. This implies that reactivation of latent virus may be an important source of clinical infection. The studies on the molecular epidemiology of CMV infections recently reported by Winston et al\(^9\) provide excellent evidence that pretransplant CMV exposure may result in CMV disease after transplant. In those studies, four patients with asymptomatic CMV excretion before transplant developed CMV infection after transplant. In each case the post–bone marrow transplant isolate was genetically identical to the pretransplant isolate. Although reactivation of CMV has not been rigorously proven in humans, other herpesviruses may be reactivated after latent periods.\(^10\) In addition, immunosuppression similar to that used in bone marrow transplantation has resulted in CMV reactivation in murine models.\(^11\) Apparent transmission of CMV by granulocytes from seropositive blood donors points to latent viruses harbored by such donors that become infective when transfused into immunosuppressed hosts.\(^12,13\) Thus it is likely that seropositive bone marrow recipients reactivate viruses that are latent in one or more body tissues. The relative contribution of other sources, such as blood transfusions, in seropositive individuals is unclear.

The bone marrow donor was not an obviously important source of CMV, since donor serology did not predict risk for development of CMV. This is in contrast to the situation in solid organ transplantation, where the transplanted kidney\(^14\) or heart\(^15\) from a positive donor may carry the virus, causing infection and disease in the recipient. Our data imply that the bone marrow from a seropositive donor is less infective than the kidney or the heart. The explanation for this difference is not clear. The infected cells may be quickly destroyed after

| Table 5. Incidence of CMV Infection According to Acute GVHD Treatment Regimen |
|---------------------------------|------------------|--------------------|
|                                | Maximal AGVHD     | CMV Infection Incidence |
|                                | Therapy           | Seronegative       | Seropositive       |
| No GVHD                         | 9/77              | 11/23              |
| GVHD, no therapy                | 0/3               | 1/1                |
| Topical steroid                 | 5/14              | 3/5                |
| Prednisone (60 mg/m²/d)         | 7/27              | 5/6                |
| Methylprednisolone (30 mg/kg/d) | 5/16              | 8/9                |

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bone marrow transplantation. Alternatively, during latency, the virus may not reside in the bone marrow in adequate numbers to be infective. It is also possible that the acquisition of CMV from other sources, such as blood products, may mask the contribution of the bone marrow donor, as suggested by the preliminary data of Bowden et al.16

Our finding that patients developing CMV infection received more transfusions before development of CMV suggests that red cell and platelet transfusions may transmit CMV in this population. Granulocyte transfusions have been clearly implicated in causing CMV infection after marrow transplant (Winston et al12 and Hersman et al13). None of our patients received granulocyte transfusions. Yeager et al19 reported that newborns receiving more than 50 pediatric blood units had a 24.4% incidence of CMV infection, but when infants received only screened CMV-negative blood products, 0/90 developed CMV infection. Preiksaitis et al,15 in a much smaller study of cardiac transplant patients, found that using only CMV-seronegative blood products reduced the incidence of posttransplant CMV. The preliminary study of Bowden et al10 also suggests that blood product screening is effective in preventing CMV in bone marrow transplant patients. These studies strengthen our impression that CMV is transmitted by red cell and platelet transfusions during the post-transplant course. The low incidence of CMV seropositivity in our blood donor population (30%) may in part explain our relatively low posttransplant CMV infection rate. A prospective study is now in progress in Minnesota to define the importance of blood transfusion in transmission of CMV infection after bone marrow transplantation.

The conditioning regimen used did not influence CMV infection rate. However, nearly all of our patients received radiation, either total body or total lymphoid. Among four patients who did not receive irradiation, no patient acquired CMV. Meyers et al10 have emphasized that irradiation (even in low doses) predisposes to CMV pneumonitis. It is apparent from our patients that there is no difference between total body and total lymphoid irradiation as far as CMV risk. Our data complement those of Meyers in suggesting that irradiation (even in low doses) predisposes to CMV infection by enhancing immunosuppression rather than by damaging CMV target organs.

The nature of the relationship between GVHD and CMV infection is important. In our patients, GVHD usually preceded CMV infection. Although it is tempting to suggest that the immunosuppressive therapy used to treat GVHD allowed CMV infection, in fact, CMV infection was associated as much with AGVHD treated topically as with AGVHD treated with high-dose bolus methylprednisolone. These data suggest that the immunosuppression associated with AGVHD is more important than anti-GVHD immunosuppressive therapy in allowing reactivation of latent virus or dissemination of virus in newly infected patients. The alternative explanation that CMV infection predisposes to GVHD appears unlikely, since GVHD preceded CMV infection in most of our patients. CMV infections have been associated with a number of immunologic alterations, however, including reversal of the T4-T8 lymphocyte ratio,18 alteration in cytotoxic T cell19 and natural killer cell20 activity, and enhanced expression of HLA-DR antigens. In addition, increased rejection of renal allografts has been associated with the presence of CMV infection.18,22 Thus CMV might enhance immune system reactivity, or it might alter the antigenicity of host tissues, thereby leading to an increased incidence of GVHD. If this is the case, prevention of CMV infection may decrease the incidence of GVHD. Indeed, Condie and O’Reilly observed a suggestive decrease in GVHD incidence when they prevented post-transplant CMV infection with prophylactic hyperimmune globulin.

The sources of CMV infections appear to differ among bone marrow transplant patients. Seropositive patients may reactivate latent virus, while seronegative patients acquire CMV from exogenous exposure, possibly from blood transfusions. Immunosuppression caused by AGVHD appears to predispose to CMV infection. Our data suggest, however, that minimizing immunosuppressive treatment of GVHD may not decrease incidence of CMV infection, but that effective GVHD prevention may have an impact on CMV infection rates. Regardless of the source, CMV infections are frequently quite serious, with significant mortality and organ dysfunction. We are currently evaluating screened seronegative blood products for prevention of CMV infection in seronegative recipients at the University of Minnesota. Reactivation may be the primary source of CMV infections in seropositive patients; prophylaxis designed to kill or suppress reactivated virus may be necessary to prevent clinical CMV disease in seropositive recipients. Immunoglobulin with high anti-CMV titer or antivirals such as acyclovir, 9-[(2-hydroxy-1-(hydroxymethyl)ethoxymethyl]guanine, or leukocyte interferon may prove useful when administered prophylactically to high-risk patients. The effectiveness of various forms of prophylaxis against CMV infection is currently under study, and we are hopeful that effective prophylaxis will improve results from bone marrow transplantation.

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