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Transfusion support using filtered unscreened blood products for cytomegalovirus-negative allogeneic marrow transplant recipients

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Summary:

It has been suggested that leukoreduced unscreened blood products can be used as an alternative to components from cytomegalovirus (CMV)-seronegative donors in order to prevent transmission of CMV from transfusions for CMV-seronegative marrow transplant recipients with CMV-seronegative donors, but confirmatory data are lacking. A retrospective chart review was undertaken for patients undergoing allogeneic transplantation over a 4-year period during which blood products were filtered for CMV-seronegative patients with CMV-seronegative donors when CMV-seronegative components were not available. Forty-five CMV-seronegative patient–donor pairs were identified. Only one patient developed CMV disease (pneumonia) and no other patients developed an infection. In this group of patients, the rate of CMV infection was 2.7% (95% CI, 0–8%) by life-table analysis. We conclude that filtered unscreened blood products as partial transfusion support for CMV-seronegative marrow transplant recipients were associated with a low incidence of CMV infection, justifying further evaluation of filtered blood products as total transfusion support for this patient population. However, since CMV infections still occur, continued surveillance by periodic culture or other techniques is warranted.

Keywords: cytomegalovirus infections; filtered blood components; bone marrow transplantation

Meyers *et al*[1] reported that 28% of cytomegalovirus (CMV)-seronegative marrow transplant recipients with CMV-seronegative donors developed CMV infections, and these were attributed to transmission of virus by leukocytes in blood components used for transfusions. Although use of blood products solely from CMV-seronegative donors was associated with a reduction in CMV infection to approximately 3% in CMV-seronegative transplant patients,[2,3] the availability of such blood products is limited by the high incidence of CMV infection in the general population. Leukoreduction by filtration has emerged as an alternative means for providing unscreened blood components with a low risk of transmission of CMV. The incidence of CMV infection is 0–2.4% in autologous and allogeneic marrow transplant recipients receiving filtered blood products as partial or complete transfusion support,[4–6] but little information is available about the efficacy of this approach in the high-risk allogeneic population alone. We report the results of our experience with partial transfusion support using filtered blood components for CMV-seronegative allogeneic marrow transplant patients with CMV-seronegative donors.

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Materials and methods

Patient population

From January 1990 to December 1993, 45 CMV-seronegative patients with CMV-seronegative donors underwent allogeneic marrow transplantation at UT MD Anderson Cancer Center. These patients account for approximately 12% of all allogeneic transplantations during this period of time. Only those patients and donors who were CMV-seronegative by serological screening using the Latex Agglutination Assay (Becton Dickinson, Cockeysville, MD, USA) and by CMV culture of the urine and blood prior to transplantation were included. Characteristics of the study population are summarized in Table 1. The majority of patients were adults with leukemia. Nineteen (42%) received T cell-depleted transplants, and 13 (29%) had alternative donors.

Transfusion support

Packed red blood cells were administered to maintain a hemoglobin >8.0 gm/dl. Single-donor platelet units or 6 units of random-donor platelets were administered once daily to maintain a platelet count $>20 \times 10^9$/l or more frequently for patients with active bleeding. During the study period, CMV-seronegative patients with CMV-seronegative donors preferentially received screened blood components, and leukofiltration was used when CMV-seronegative components were not available. Blood components that were screened for CMV antibodies were tested using the standard Latex Agglutination Assay.

Leukoreduction of components

Platelet concentrates were administered through a Sepacell PL-10A or PLS-10A leukocyte reduction administration set

Table 1 Characteristics of marrow transplant recipients and donors

Recipients	
Number	45
Sex M/F	30/15
Median age (range) years	31 (2–54)
Diagnosis	
Aplastic anemia	3
Myelodysplasia	1
Acute leukemia	14
Chronic leukemia	19
Myeloma	2
Lymphoma	5
Hodgkin's disease	1
Preparative regimen	
TBI-containing	33
Chemotherapy alone	12
Graft-versus-host disease prophylaxis	
Tacrolimus + methotrexate	1
Cyclosporine + methotrexate	14
Cyclosporine + other	11
T cell depletion + cyclosporine ± other	19
Outcomes (95% CI)	
Grades 2–4 graft-versus-host disease %	54 (38–70)
Day-100 survival %	60 (45–75)
2-year survival %	38 (23–52)
CMV infection %	2.7 (0–8)
Donors	
Sex M/F	29/16
Median age (range) years	29 (4–57)
HLA compatibility	
Matched related donor	32
Mismatched related donor	2
Matched unrelated donor	11

(Fenwal Division, Baxter Corporation, Deerfield, IL, USA). Packed red blood cells were administered through Sepacell R-500 leukocyte reduction filters (Fenwal Division). Filtration was performed in the blood bank or at the bedside with quality control testing as described.[7] Leukocyte count, platelet count, and hematocrit were measured in aliquot sample before and after filtering using a Coulter JTS (Miami, FL, USA). Absolute values of each were calculated by multiplying the concentration times of the volume of the component. For quality control, leukocyte counts were also performed with a Nageotte chamber using a 1:5 dilution of platelet concentrates and a 1:10 dilution of packed red blood cells in 0.0025% propidium iodide.[7] Filtered components were expected to have $<1 \times 10^6$ residual leukocytes/unit. Hemoglobin and platelet recoveries were expected to exceed 80%.

CMV prophylaxis and surveillance

Patients received acyclovir 5 mg/kg i.v. every 8 h to engraftment, then 400 mg orally twice daily to day 100. Intravenous immunoglobulin 500 mg/kg i.v. was administered weekly until day 100. Urine and peripheral blood buffy coat cells were collected pretransplant and at weekly intervals to day 100. The samples were tested for CMV by standard culture and shell vial assay. For diagnosis of CMV disease, bronchoalveolar lavage fluid or tissue biopsies were cultured similarly. Tissue biopsies and autopsy specimens were examined by light microscopy, immunocytochemistry or by *in situ* hybridization for CMV. CMV infection was defined as a positive surveillance culture with or without signs of disease. CMV disease was defined as a positive culture associated with pneumonitis or positive tissue biopsy.

Results

The 45 patients received a median of 36 units of packed red blood cells, 90 units of random-donor platelets, and 15 units of single-donor platelets (Table 2). Of these transfusions, filtering was used for all of the packed red blood cells, all of the random-donor platelets and all of the single-donor platelets.

Only one patient developed a CMV infection; by life table analysis, the incidence of CMV infection was 2.7% (95% CI 0–8%). The patient was a 22-year-old male with chronic myelogenous leukemia who received a T cell-depleted marrow graft from an HLA-matched sibling. Transfusion support for this patient included 25 units of packed red blood cells (24 screened and filtered and 1 filtered alone), 110 units of random-donor platelets (98 screened and filtered and 12 filtered alone), and 4 units of single-donor platelets (2 screened and filtered and 2 filtered alone). Grade 2 GVHD occurred on day 12 post-transplant, and this responded to treatment with high-dose steroids. Bilateral interstitial infiltrates were noted on day 43 post-transplant. By shell vial assay, bronchoalveolar lavage fluid and urine were positive for CMV on day 46, and blood buffy coat was positive on day 53. The patient was treated with ganciclovir and intravenous immunoglobulin with eradication of the CMV. He is currently alive and well more than 5 years post-transplant.

Discussion

The purpose of our study was to determine the safety of using filtered unscreened blood products as an alternative to CMV-seronegative components for CMV-seronegative allogeneic marrow transplant patients. The actuarial risk of CMV infection and disease was 2.7%, and there was no CMV-related mortality. A similar rate of infection was reported by Bowden *et al*,[6] although a direct comparison to our study cannot be made, since a substantial proportion of those patients had undergone autologous transplantation, a population with a lower risk of CMV infection.[8] van Prooijen *et al*[9] reported no CMV infections after allogeneic marrow transplantation for CMV-seronegative recipients administered only filtered unscreened blood components, but their sample size was too small to detect a low infection rate. Taken together, these results support the use of filtered unscreened blood products for CMV-seronegative allogeneic transplant patients, with the caveat that surveillance for CMV is still required for early detection of infections that may occur at a low rate.

The acceptance of filtered blood components to prevent transmission of CMV[10] required that this approach result in an infection rate no higher than that with screened blood products. Transfusion-associated CMV infection may still

Table 2 Transfusion support

Component	*No. of patients*	*Units/Patient transfused*	*Units/Patient CMV screened and filtered*	*Units/Patient CMV filtered only*
Packed red blood cells	44	36[a] (1–150)	32 (3–150)	11 (1–41)
Random donor platelets	41	90 (4–692)	97 (4–462)	31 (4–96)
Single donor platelets	43	15 (1–74)	14 (1–74)	20 (1–29)

[a]Number (range).

occur when using screened blood products. Although this may be a consequence of false negative results with the current serological tests for CMV antibodies, albeit at a very low rate, some individuals may have early or asymptomatic infections and have not yet seroconverted at the time of donation. Indeed, in a prospective study by Wilhelm *et al*,[11] volunteer blood donors had a 0.8% annual seroconversion rate.

Primary CMV infection may also occur as a result of respiratory tract-mediated transmission from a community source. Although we cannot exclude community acquired CMV infection in our patients who developed CMV pneumonia, the standard infection precautions utilized by our patients should make this possibility remote.

Successful use of filtration to prevent transfusion-associated CMV infection depends on the adequacy of depletion of leukocytes during the procedure. It should be noted that our quality control program required that the filtration procedure allowed no more than $<1 \times 10^6$ leukocytes/unit after filtration. This is lower than the current standard ($<5 \times 10^6$ residual leukocytes/unit) and clearly feasible with the filters available. Consequently, with the appropriate quality control measures in place, our results will likely be applicable to other institutions and will allow this approach to be used for other populations at high risk for transfusion-associated infections.[10,12]

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