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Post-transplant events

Transfusion of leukoreduced cellular blood components from cytomegalovirus-unscreened donors in allogeneic hematopoietic transplant recipients: analysis of 72 recipients

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Summary:

Leukoreduction of blood components has been considered a safe alternative to screening donors for CMV. The objective of this study is to analyze the effectiveness of bedside leukoreduction in preventing CMV transmission. We retrospectively studied 72 transplant recipients and donors who were CMV-seronegative pairs. All patients were transfused with CMV-unscreened cellular blood products leukoreduced at the bedside using leukoreduction filters. Quality control measures performed monthly in our leukoreduced blood components consistently demonstrated that at least 95% of the units sampled meet the leukoreduction criterion established by the American Association of Blood Banks standards. The CMV status of the recipients and donors was determined before transplantation by the latex agglutination assay. Recipients were observed for at least 100 days after transplantation. CMV cultures of urine, buffy coat, bone marrow, and bronchial washings were done weekly when indicated. CMV antigenemia testing was performed twice weekly: 11 transplant recipients seroconverted after transplantation. One patient was positive for CMV antigenemia 4 months after transplantation, but did not have CMV infection. Two of 61 patients who were not seroconverted were CMV antigenemia positive and did not have CMV infection: leukoreduction of cellular blood products is an efficient method of preventing CMV infection.
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Over the past 5 years, the number of hematopoietic transplants performed in both adults and children has increased to treat malignant and nonmalignant hematologic conditions. BMT is still considered the treatment of choice for many hematological malignancies and severe hematopoietic and immune disorders.[1] However, some complications of this procedure are still encountered, such as infection, graft-versus-host disease (GVHD), drug-induced lung disease, transient pulmonary hemorrhage, and recurrent malignancy.[2,3]

CMV continues to be associated with post transplantation morbidity and mortality. Drugs used for prophylaxis and treatment of CMV infection can cause pancytopenia and impair renal function, adding to the complexity of this scenario. In addition, the increasing use of donors other than HLA-identical siblings has led to delayed immune recovery and increased incidence of complications associated with GVHD and CMV infection and reactivation. CMV infection may also be associated with the development of chronic allograft dysfunction and graft loss.[4,5]

One measure for preventing CMV infection in recipients of hematopoietic stem cell transplants with CMV-seronegative donor–recipient pairs is leukoreduction of cellular blood components. Use of CMV-seronegative donors is often limited by their availability. As of this date, leukoreduction is the only available alternative to solving the problem of supporting CMV-seronegative transplant recipients given the limited availability of CMV-seronegative donors. Furthermore, false-negative serological results for CMV infection in blood donors have been reported.[6,7]

We describe herein a study that is part of an ongoing quality control and improvement process in evaluating the effectiveness of leukoreduction of cellular blood products to prevent CMV infection in patients who are CMV seronegative and have received hematopoietic transplants from CMV-seronegative donors. In this study, we report the outcome of 72 hematopoietic transplant recipients with transplant donors who are CMV seronegative and had received cellular blood products from CMV unscreened volunteer donors.

Materials and methods

All patients who received allogeneic hematopoietic stem cell transplants at our institution from January 2002 to March 2004 were analyzed retrospectively. All CMV-seronegative

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transplant recipients and healthy donor pairs were included. All of the patients had been transfused with blood components that were not screened for CMV antibody. Platelet concentrates were infused through a leukoreduction filter (Sepacell PL-10A or PLS-10A leukocyte reduction administration set; Baxter, Deerfield, IL, USA), whereas RBC units were administered through a Sepacell R-500 leukocyte reduction filter (Baxter). Filtering was performed at the bedside.

All of the patients and donors were screened for their CMV status by using a latex agglutination assay before transplantation. CMV cultures of the patients' urine, buffy coat, bone marrow, and bronchial washings were done weekly when indicated. CMV antigenemia was tested using a direct immunofluorescence assay on buffy coat preparation of white blood cells (WBC). This was performed twice weekly until the patient was discharged. CMV-positive cells were normalized according to the number of WBCs per million. After the patients were discharged, their primary care physicians were requested to monitor their CMV antigenemia testing once a week by using the technology available in their respective laboratories.

CMV prophylaxis

The current standard of care for CMV infection at our institution is pre-emptive therapy, in which antiviral treatment is initiated only when a viral infection is documented. Therefore, all patients are screened twice weekly with the use of CMV antigenemia testing. However, for patients considered at risk for CMV infection, prophylaxis with an antiviral agent is initiated. The patients who fall into this category are recipients of haploidentical transplants, recipients of alemtuzumab (Campath) in their conditioning regimen, and recipients of high-dose steroids (>2 mg/kg methylprednisolone) for the treatment of GVHD. These patients also receive foscarnet for the prevention of CMV infection. This strategy is employed irrespective of the donor and recipient's CMV serostatus. In our study, intravenous immune globulin (IVIg) at a dose of 0.2 gm/kg was administered weekly from the week of transplantation to 100 days after transplantation as a prophylactic measure.

Definitions

CMV infection was defined as documentation of CMV-positive cultures from suspected sites. CMV disease was defined as a CMV-positive culture plus clinical illness or a CMV-positive tissue biopsy sample.[8] The medical records of patients who seroconverted and those with CMV-positive antigenemia were reviewed. Tissues and fluids, such as urine and bronchoalveolar lavage samples, that were cultured were followed and investigated.

Results

We included 72 CMV-seronegative patient/donor pairs in this study. The donor and recipient were unrelated in 38 cases, which included one cord blood transplant, and related in 34 cases.

Table 1 Patient characteristics

Characteristic	*Number of patients*
Median age, years (median)	30 (4–57)
Sex	
Female	44
Male	28
Stem cell source	
BM	40
Peripheral blood	27
Cord blood	1
Underlying disease	
CML	13
Lymphoma	12
AML	11
Hodgkin's lymphoma	5
CLL	5
ALL	5
T-cell lymphoma	4
Myelodysplastic syndrome	4
Renal cell cancer	2
Myelofibrosis	2
Mycosis fungoides	2
Multiple myeloma	1
Refractory anemia with excess blasts	1
T-cell promyelocytic leukemia	1
Aplastic anemia	1
Breast cancer	1
Acute promyelocytic leukemia	1
Metastatic colon cancer	1

Table 2 Blood products transfused before and after transplantation

Blood product	*Number of patients*	*Mean number of transfusions (range)*
Random donor platelets	58	13.55 (1–92)
Packed RBCs	49	12.67 (1–54)
IVIg	48	3.95 (1–28)
Single-donor platelets	44	3.84 (1–27)
Fresh-frozen plasma	4	8.50 (2–15)
Cryoprecipitate	1	1

Patient characteristics are shown in Table 1. All of the patients received blood components, including IVIg, after transplantation (Table 2). Specifically, 68% of the patients received red blood cells (RBCs), 81% received random donor platelets (RDP), 61% received single donor platelets (SDP), 1% received cryoprecipitate, 6% received fresh frozen plasma, and 67% received IVIg. We did not perform granulocyte transfusions in this cohort.

We identified 11 transplant recipients who seroconverted after transplantation. One was positive for CMV antigenemia 4 months after transplantation but did not have CMV infection. In comparison, two of the 61 patients who did not seroconvert were positive for CMV antigenemia. These two patients did not have CMV infection.

Discussion

The results of this study confirm our previous observations that leukoreduction of cellular blood products from CMV-

unscreened donors is an acceptable strategy for providing cellular blood components to CMV-seronegative recipients of hematopoietic stem cell transplants from CMV-seronegative donors.[8,9] This is extremely helpful, especially in a setting with a very limited number of donors who are CMV seronegative.

Of note, is our observation that not one of the 72 transplant recipients had CMV infection. Also, the seroconversion observed in 11 patients after transplantation could be attributed to receiving IVIg. Furthermore, one case positive for CMV antigenemia may have been false-positive. This patient had CMV antigenemia 106 days after BMT with only two cells per million of WBCs positive for CMV at the time of CMV antigenemia testing. Interestingly, two of the transplant recipients who had not seroconverted had CMV antigenemia; these cases were considered true positives. Although these two patients did not have full-blown CMV infection, the presence of CMV antigenemia may be a good indicator for early infection.

In a previous study of 100 patients who received an infusion of granulocytes obtained from CMV-unscreened donors, we found that 4% of the patients had CMV infection, although these patients were CMV seropositive prior to their transfusion.[10] In a similar study of 142 patients, Vij *et al*[11] also showed that the donors' CMV status had no impact on the incidence of CMV viremia or disease.

Judging from both of these previous studies, CMV antibody testing does not seem to be a good indicator in predicting the development of CMV infection in these cancer patients. Because of immunosuppression, the titer of the CMV antibody in patients with cancer may be undetectable with our current testing methodology. This may explain the CMV status in some patients who we found to be CMV-antibody reactive at some point but not CMV-antibody reactive later. However, the results of several studies analyzing the effect of CMV antibodies on the outcome of CMV infection in bone marrow transplant recipients were inconclusive.[12–14]

The new-generation leukoreduction filters remove approximately 99% of WBCs. In addition to the improved system of quality control in WBC counting, use of these filters has rendered the potential risk of CMV transmission in blood components negligible. Currently, the American Association of Blood Banks standards require preparation of leukoreduced components by a method known to reduce the leukocyte number to $<5\times10^6$. We perform quality control measures monthly to demonstrate that at least 95% of the sampled units meet this criterion.[15] Different methods of leukoreduction, such as prestorage filtration at the bedside during infusion, have been employed to comply with this standard.

Conclusion

In this study, we showed that the use of leukoreduced cellular blood products with consistent close monitoring of the quality of the leukoreduction is an efficient method of preventing CMV infection in bone marrow transplant recipients. In addition, we demonstrated that CMV antibody testing is not ideal for screening donors for CMV. More studies are needed to further evaluate other tests that may be used in place of current CMV antibody testing.

References

1 Delgado R, Lumbreras C, Alba C *et al*. Low predictive value of polymerase chain reaction for diagnosis of cytomegalovirus disease in live transplant recipients. *J Clin Microbiol* 1992; **30**: 1876–1878.
2 Reusser P, Riddell SR, Meyers JD, Greenberg PD. Cytotoxic T-lymphocyte response to cytomegalovirus after human allogeneic bone marrow transplantation: pattern of recovery and correlation with cytomegalovirus infection and disease. *Blood* 1991; **78**: 1373–1380.
3 Ettinger NA. Pulmonary considerations of organ transplantation. Part 2. *Am Rev Respir Dis* 1991; **144**: 213–223.
4 Duncan SR, Paradis IL, Yousem SA *et al*. Sequelae of cytomegalovirus pulmonary infections in lung allograft recipients. *Am Rev Respir Dis* 1992; **146**: 1419–1425.
5 Siad G, Patel R. New strategies for prevention and therapy of cytomegalovirus infection and disease solid-organ transplant recipients. *Clin Microbiol Rev* 2000; **13**: 83–121.
6 Larsson S, Soderberg-Naucler C, Wang F-Z *et al*. Cytomegalovirus DNA can be detected in peripheral blood mononuclear cells from all seropositive and seronegative healthy blood donors over time. *Transfusion* 1998; **38**: 271–278.
7 Zhang LJ, Hanff P, Rutherford C *et al*. Detection of human cytomegalovirus DNA, RNA and antibody in normal donor blood. *J Infect Dis* 1995; **171**: 1002–1006.
8 Narvios AB, Przepiorka D, Tarrand J *et al*. Transfusion support using filtered unscreened blood products for cytomegalovirus-negative allogeneic marrow transplant recipients. *Bone Marrow Transplant* 1998; **22**: 575–577.
9 Narvios A, Lichtiger B. Bedside leukoreduction of cellular blood components in preventing cytomegalovirus transmission in allogeneic bone marrow transplant recipients: a retrospective study. *Haematologica* 2001; **86**: 749–752.
10 Narvios A, Pena E, Han XY, Lichtiger B. Cytomegalovirus infection in cancer patients receiving granulocyte transfusions. *Blood* 2002; **99**: 390–391.
11 Vij R, DiPersio J, Venkatraman P *et al*. Donor CMV serostatus has no impact on CMV viremia or disease when prophylactic granulocyte transfusions are given following allogeneic peripheral blood stem cell transplantation. *Blood* 2003; **101**: 2067–2069.
12 Meyers JD. Prevention of cytomegalovirus infection after marrow transplantation. *Rev Infect Dis* 1989; **11** (Suppl. 7): S1691–S1705.
13 Neiman PE, Reeves W, Ray G *et al*. A prospective analysis of interstitial pneumonia and opportunistic viral infection among recipients of allogeneic bone marrow grafts. *J Infect Dis* 1977; **136**: 754–767.
14 Boland GJ, Vlieger AM, Ververs C, de-Gast GC. Evidence for transfer of cellular and humoral immunity to cytomegalovirus from donor to recipient in allogeneic bone marrow transplantation. *Clin Exp Immunol* 1992; **88**: 506–511.
15 Gorlin JB (ed). *Standards for Blood Banks and Transfusion Services*. 21st edn, American Association of Blood Banks: Bethesda, MA, 2002, p 29.