

## **Safety of leukoreduced, cytomegalovirus (CMV)-untested components in CMV-negative allogeneic human progenitor cell transplant recipients**

Transfusion-transmitted cytomegalovirus (TT-CMV) infection can lead to significant morbidity and mortality in CMV-negative (CMV-N) hematopoietic progenitor cell (HPC) transplant patients. In 1995, Bowden and colleagues<sup>1,2</sup> demonstrated the efficacy of leukoreduced components to reduce TT-CMV in most high-risk populations, although there remained safety concerns in CMV-N allogeneic HPC transplant recipients. As a result, several transplant programs recommended both leukoreduced and CMV-N components for CMV-N allogeneic HPC patients receiving transplants from CMV-N donors (CMV<sup>neg/neg</sup>).<sup>2</sup> A more recent study, however, has challenged the clinical benefit of requiring CMV-N, in addition to leukoreduction, in CMV<sup>neg/neg</sup> HPC patients. In a 10-year study, Thiele and colleagues<sup>3</sup> found no cases of TT-CMV in 23 CMV<sup>neg/neg</sup> HPC patients transfused with 1847 CMV-untested (CMV-U), leukoreduced components. We would like to share our institution's experience in 100 CMV<sup>neg/neg</sup> allogeneic HPC patients transfused with 6465 CMV-N and CMV-U cellular components.

Before July 2006, the University of Michigan provided, when available, CMV-N components to all CMV<sup>neg/neg</sup> HPC transplant recipients. A preliminary 12-month retrospective review showed that 52% (14/27, 2004) had received leukoreduced, CMV-U blood components due to shortages in CMV-N products, with no cases of TT-CMV.<sup>4</sup> As a result, the transfusion policy was changed in mid-2006 to provide leukoreduced, CMV-U products for all HPC patients, regardless of pretransplant CMV status. For quality assurance, we monitored the CMV conversion rate over a 36-month period (January 2005 to December 2007) covering an 18-month period before and after the change in transfusion policy (Table 1). Per institutional practice, CMV-N patients were screened for CMV IgG every 1 to 2 months pretransplant, followed by regular testing for CMV nucleic acid testing (NAT) after transplant. The minimum posttransplant follow-up was 12 months. All blood products were provided by Southeast Michigan American Red Cross (Detroit, MI) and were leukoreduced after storage (Leukotrap RC system, Pall Corp., Port Washington, CA).

As shown in Table 1, 100 patients were available for analysis and included both adult and pediatric patients. All patients were CMV-N before transplant, received a CMV<sup>neg/neg</sup> allogeneic HPC transplant, and underwent weekly posttransplant CMV NAT monitoring. Except for sex, there were no significant differences in patient demographics, transplant type, or transfusion support in

the two study cohorts. In the CMV-N policy period, only 11% to 15% of cellular components were CMV-N, with most patients receiving a mix of CMV-N and CMV-U. Only five patients received 100% CMV-N products. All five patients had low transfusion needs, requiring 2 to 10 red blood cell (RBC) and two to three platelet (PLT) transfusions.

Two adult male patients had a single positive test for CMV IgG at 3 and 5 weeks after transplant, respectively (Table 1). Both patients tested negative for CMV IgM and CMV NAT and had no evidence of clinical CMV infection. Each patient received between 42 and 45 CMV-U cellular components in the weeks before seroconversion: neither patient had received intravenous immune globulin before CMV IgG testing. There were no CMV seroconversions in the CMV-U period. The overall CMV IgG seroconversion rate was 2% per patient and 0.03% per unit, which is comparable to the findings by Bowden and coworkers<sup>1</sup> (2.4% per patient, 0.023% per component). The rate of confirmed TT-CMV was 0%, consistent with the study by Thiele and coworkers<sup>3</sup> and lower than that reported by Wu and coworkers<sup>5</sup> (6.5% per patient, 0.23% per CMV-positive component). As discussed by Thiele and Wu, the CMV IgG detected in our patients likely represents passive antibody from recent transfusions.<sup>3,5</sup>

Our findings confirm those of Thiele and affirm the equivalent safety of CMV-U, leukoreduced components in CMV<sup>neg/neg</sup> allogeneic HPC patients.<sup>3</sup> The absence of clinical TT-CMV infection in our study and that by Thiele and coworkers,<sup>3</sup> despite the combined transfusion of nearly 8000 CMV-U, leukoreduced components, contradicts sentiments from a past multivariate analysis, which advocated continued provision of CMV-N and leukoreduced components for CMV<sup>neg</sup> transplant patients.<sup>6</sup> The improved safety of CMV-N over CMV-U, leukoreduced is also not supported by a recent large prospective study of 34,000 blood donors. Ziemann and colleagues<sup>7</sup> found CMV viremia only among newly seroconverted donors and a few CMV-N donors, arguing that CMV-N components may present the higher risk of TT-CMV due to passive transfusion of free CMV DNA. In summary, policies stipulating leukoreduced, CMV-N components in CMV<sup>neg/neg</sup> allogeneic HPC patients do not confer additional safety and are limited by product shortages and significant transfusion support required by many allogeneic HPC patients.

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TABLE 1. Transfusion support in CMV<sup>neg/neg</sup> allogeneic HPC transplant patients

| Measure                              | CMV policy period (year)                  |                                 | p value* |
|--------------------------------------|---|---------------------------------|----------|
|                                      | All patients (January 2005-December 2008) | CMV-U (July 2007-December 2008) |          |
| Patient demographics                 |   |                                 |          |
| Number of patients                   | 100                                       | 54                              | NS       |
| Sex                                  |   |                                 |          |
| Male                                 | 58  | 40                              | 0.0004   |
| Female                               | 42  | 14                              |          |
| Age                                  |   |                                 |          |
| Adults                               | 85  | 45                              | NS       |
| Pediatric                            | 15  | 9                               |          |
| Underlying disease                   |   |                                 |          |
| Leukemia/MDS                         | 65  | 33                              | NS       |
| Multiple myeloma                     | 4   | 3                               | NS       |
| Lymphoma                             | 28  | 15                              | NS       |
| Other†                               | 3   | 3                               | NS       |
| Transplant type                      |   |                                 |          |
| Matched, related                     | 46  | 25                              | NS       |
| Matched, unrelated                   | 54  | 29                              | —        |
| ABO identical                        | 52  | 32                              | NS       |
| ABO nonidentical                     | 48  | 22                              | —        |
| HPC source                           |   |                                 |          |
| HPC-apheresis                        | 84  | 43                              | NS       |
| HPC-marrow‡                          | 13  | 9‡                              | NS       |
| HPC-cord‡                            | 4   | 3‡                              | NS       |
| Transfusion support                  |   |                                 |          |
| RBC transfusion                      |   |                                 |          |
| Number of patients transfused        | 87  | 44                              | NS       |
| Total number of units                | 805                                       | 399.5                           | —        |
| Units/patient§ (median, range)       | 83.1 ± 1.1 (5,0-58)                       | 7.5 ± 1.2 (5, 0-40)             | NS       |
| % CMV-N                              | NA  | 15.7%                           | —        |
| PLT transfusion                      |   |                                 |          |
| Number of patients transfused        | 88  | 46                              | NS       |
| Total number of units                | 5660                                      | 2376                            | —        |
| Units/patient§ (median, range)       | 57.7 ± 11.6 (0-819)                       | 45.7 ± 8.5 (25, 0-309)          | NS       |
| % CMV-N                              | NA  | 11.3%                           | —        |
| Cellular blood product support       |   |                                 |          |
| Number of patients transfused        | 92  | 50                              | NS       |
| Total number of units (RBCs, PLTs)   | 6465                                      | 2775.5                          | —        |
| Total units/patient§ (median, range) | 61.9 ± 12 (25, 0-877)                     | 52.4 ± 9.4 (30, 0-338)          | NS       |
| CMV seroconversion**                 |   |                                 |          |
| Number of patients                   | 2   | 2                               | —        |

\* Significance determined by t test and chi-square. A p value of less than 0.05 was considered significant.

† Includes sickle cell anemia,  $\beta$ -thalassaemia, severe combined immunodeficiency.

‡ One pediatric patient received both HPC-marrow and HPC-cord from the same related donor.

§ Results reported as mean  $\pm$  SEM, median and range.

|| PLTs were whole blood derived, prestorage leukoreduced PLT concentrates and contained fewer than  $8.3 \times 10^5$  white blood cells (WBCs) per unit and fewer than  $5 \times 10^6$  WBCs per 5-unit pool. Each adult transfusion contained five pooled PLT concentrates. Pooled PLTs containing at least one CMV-U unit were labeled and dispensed as CMV-U.

¶ Higher mean PLT usage was due to five patients who required greater than 250 PLTs.

\*\* Patients tested positive for CMV IgG. Patients were negative for CMV IgM and CMV NAT. MDS = myelodysplastic syndrome; NA = not available; NS = not significant ( $p > 0.05$ ).

## CONFLICT OF INTEREST

The authors certify that they have no affiliation with or financial involvement in any organization or entity with a direct financial interest in the subject matter or materials discussed in this manuscript.

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## Does modern combat still need fresh whole blood transfusions?

In combat, massive blood loss of military as well as of civilians is a major cause of death. Having blood available in the military theater at all times is therefore of vital importance. Fresh whole blood (FWB) has been used repeatedly by the US military to resuscitate severely bleeding trauma patients.<sup>1</sup> FWB is blood that is donated by military and hospital personnel on site and stored for less than 24 hours in citrate-phosphate-dextrose solution at room temperature. The US military supports transfusion of FWB either when standard blood components are not available or if transfusion of the available blood components are not adequately correcting life-threatening bleeding. Although warm FWB has the theoretical advantage of supplying all the appropriate blood components with maximal functionality, usage of untested FWB proposes a risk of infectious disease transmission and bacterial contamination as well as logistic difficulties in obtaining identical match donors at the right time. Transfusion of FWB has also been associated with a higher incidence of adverse reactions through the presence of white blood cells (WBCs). These reactions include febrile nonhemolytic transfusion reactions, human leukocyte antigen alloimmunization and transfusion-associated graft-versus-host disease (TA-GVHD).<sup>2</sup> Hence, in a recent article by Gilstad and colleagues<sup>3</sup> clinical symptoms of TA-GVHD were observed in a trauma patient who was resuscitated with FWB.

Usage of FWB is often endorsed because of the potential damaging effects of prolonged refrigerated stored RBCs. Yet, frozen storage of RBCs at ultralow temperatures halts the cellular metabolism and subsequently prevents the progressive RBC deterioration that has been linked to adverse clinical outcome.<sup>4</sup> During the years, frozen blood components have become more utilizable. Notably, implementation of frozen platelets (PLTs) and fresh-frozen plasma in transfusion medicine has abandoned the need for FWB usage. Consequently, in 2001 the Dutch military blood bank eliminated the use of FWB on site and implemented the routine usage of universal frozen blood components.<sup>5,6</sup> In this regard, leukoreduced blood components are frozen at  $-80^{\circ}\text{C}$  within 24 hours after collection. After thaw, RBCs, fresh-frozen plasma, and PLTs can be utilized up to 14 days, 7 days, and 6 hours, respectively. The Dutch military has demonstrated that frozen blood components can provide an adequate blood resource, even when standard blood components cannot be replenished on time. This allows for a better inventory control, especially in remote or primitive locations.

Usage of frozen blood components has the advantage that it is safe. This is because blood components have been collected and preserved under standard conditions