Comparison of Immune Reconstitution After Unrelated and Related T-Cell–Depleted Bone Marrow Transplantation: Effect of Patient Age and Donor Leukocyte Infusions


Unrelated bone marrow transplantation (BMT) is often complicated by fatal opportunistic infections. To evaluate features unique to immune reconstitution after unrelated BMT, the lymphoid phenotype, in vitro function, and life-threatening opportunistic infections in vitro propagated viral specific T cells were analyzed longitudinally and compared. The effects of posttransplant donor leukocyte infusions to treat or prevent cytomegalovirus (CMV) or Epstein-Barr virus (EBV) infections on immune reconstitution were also analyzed. This study demonstrates that adult recipients of unrelated BMTs experience prolonged and profound deficiencies of CD3+, CD4+, and CD8+ T-cell populations when compared with pediatric recipients of unrelated BMT and adults after related BMT (P < .01), that these adults have a significantly increased risk of life-threatening opportunistic infections, and that the rate of recovery of CD4 T cells correlates with the risk of developing these infections. Recovery of normal numbers of CD3+, CD8+, and CD4+ T-cell populations is similar in children after related or unrelated BMT. This study also demonstrates that adoptive immunotherapy with small numbers of unirradiated donor leukocytes can be associated with rapid restoration of CD3+, CD4+, and CD8+ T-cell numbers, antigen-specific T-cell responses, and resolution of CMV- and EBV-associated disease after unrelated TCD BMT.

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PATIENTS AND METHODS

For this study, we reviewed 71 consecutive patients at this institution who received an unrelated BMT depleted of T cells by soybean agglutination followed by sheep red blood cell rosetting between January 17, 1992 and August 8, 1997. These transplants were administered for the treatment of a hematologic malignancy (n = 66), aplastic anemia (n = 3), paroxysmal nocturnal hemoglobinuria (n = 1), or familial erythrophagocytic lymphohistiocytosis (FEL; n = 1). Characteristics of these patients are summarized in Table 1. All patients received cyclophosphamide (60 mg/kg/dose for 2 days). Posttransplant rejection prophylaxis consisted of 2 to 4 doses of ATG at 30 mg/kg/dose with 2 mg/kg of methylprednisolone. Posttransplant rejection prophylaxis included 5 doses of ATG at 15 mg/kg every other day, from day +5 to day +13. Both groups received 2 mg/kg/dose of methylprednisolone daily from day +5 through day +13, with rapid subsequent taper, unless GVHD developed. Since 1993, all cytomegalovirus (CMV)-seropositive patients or those with CMV-seropositive donors have received...
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pretransplant to 77 adult recipients of an HLA-related BMT and posttransplant to 65. We have previously found that patients less than 15 years of age transplanted with an HLA-matched sibling graft are not at risk for graft rejection or graft failure.39 Because of this finding, only 1 pediatric recipient (age, 16 years) received ATG and steroids after his matched sibling TCD graft. The characteristic of the HLA-matched related transplant recipients are shown in Table 1.

**Cell preparations.** Heparinized blood was collected monthly from patients for the first 3 months when possible. Thereafter, samples were obtained every 2 to 6 months until normalization of immune function and phenotype was observed. Patients were studied only once during each time period. PBMC were isolated by Ficoll-Hypaque density gradient separation.

**Immunoassays.** Two sample comparison for continuous data were analyzed to estimate the probability of opportunistic infection. Comparisons of covariates age and donor type. The marginal regression coefficient of the HLA-matched related transplant recipients are shown in Table 1.

**RESULTS**

The median nucleated cell dose per kilogram for the unrelated and related SBA E− transplant recipients were 2.74 × 10^7/kg (range, 1.01 to 14.28 × 10^7/kg) and 2.2 × 10^7/kg (range, 0.1 to 14.1 × 10^7/kg), respectively (P < .01). For the 62 evaluable recipients of an unrelated SBA E− BMT, the median time (range) to engraftment (neutrophil count >500 cells/µL) was 12 (8 to 24) days. There were no statistically significant differences in the time to reach an absolute lymphocyte count of 500 and 1,000 cells/µL after unrelated or related SBA E− BMT. Of the unrelated transplant recipients who achieved a circulating lymphocyte count of 500 (n = 58) and 1,000 cells/µL after unrelated or related SBA E− BMT. Recovery of normal to increased numbers of circulating NK cells occurred in the majority of patients by 1 month posttransplant regardless of donor type or patient age. In contrast, CD3+ and CD8+ T-cell recovery was affected both by donor type and patient age. Adult recipients of an unrelated SBA E− transplant experienced prolonged CD3+ and CD9 T-cell lymphopenia when compared with children after unrelated BMT and adults after related BMT (P < .01). Children who received an unrelated BMT had significantly decreased CD3+ and CD8+ T-cell numbers during the first 12 posttransplant months compared with those who received an HLA-matched sibling transplant (P < .01). After these early time points, CD3+ T-cell recovery was similar in both groups of children, despite ATG prophylaxis in the unrelated transplant group only (Fig 1, middle and lower panels).

Before donor leukocyte infusions, 16 of 62 patients (27%) developed acute GVHD (19% of children v 31% of adults). Five patients developed grade I acute GVHD, 7 developed grade II GVHD, and 4 developed grade III-IV acute GVHD. Of the 16 patients who developed acute GVHD, graft rejection prophylaxis with ATG was administered pretransplant in 12 and posttransplant in 4. Four patients succumbed to complications of acute GVHD, all with grade III-IV. CD3+ T-cell recovery was not significantly different in patients with or without GVHD (Fig 2). For children who received an HLA-matched versus HLA-mismatched unrelated BMT, no differences in recovery of CD3+ T-cell populations were observed (Fig 3, upper panel). Although the group size for adults was small, there was a trend toward more profound and prolonged CD3+ T
lymphopenia in the HLA disparate adult transplant group (Fig 3, lower panel).

Significant differences were noted in the recovery of CD4⁺ lymphocyte numbers not only between children and adult recipients of an SBA⁺E⁻ unrelated BMT ($P = 0.07$), but also between adults given a related or unrelated transplant ($P < 0.01$). The majority of adults had CD4 cell counts of less than 100 cells/µL for at least 6 months post transplant, with counts less than 200 cells/µL persisting for 12 to 18 months (Fig 4, upper panel). Although most children had low CD4 cell counts for the first 4 months after an unrelated BMT, the majority developed CD4 cell counts greater than 200 cells/µL by 6 months and normal numbers within 6 to 12 months post-BMT. Within the CD4 cell population, CD45Ra reconstitution (Fig 4, lower panel) was appreciably delayed in adult recipients of both related and unrelated SBA⁺E⁻ BMT compared with pediatric recipients of an unrelated transplant ($P < 0.01$). After the initial 6 months posttransplant ($P < 0.01$), no differences were observed in the recovery of CD4 or CD4⁺CD45RA populations between children who received an unrelated compared with a related SBA⁺E⁻ BMT. In children and adults, recovery of CD4 cell counts was similar regardless of whether the unrelated donor was HLA-matched or mismatched (Fig 5).

As shown in Fig 6, the majority of adult patients had persistently low PHA responses (<25% of normal) for the first 12 months posttransplant, regardless of donor type. In contrast,
Most children normalized their PHA response by 9 to 12 months after unrelated BMT. Antigen-specific responses were analyzed in 16 patients after vaccination with tetanus toxoid ($n = 16$) or after clinical reactivation of varicella virus in 4. Patients received 3 doses of tetanus toxoid at 2-month intervals starting at a median (range) of 16.7 (10.7 to 41.9) months post-BMT. Specific T-cell proliferative responses against tetanus antigen were present in all 16 patients vaccinated, with 15 of 16 developing protective tetanus antitoxin titers after the third vaccination. After clinical *Herpes zoster* infection, all 4 patients developed a proliferative response to varicella antigen that was negative before reactivation.

The infectious complications, including EBV-LPDs, that occurred after durable engraftment after unrelated SBA- E- BMT were analyzed. Thirty-four percent of unrelated transplant recipients (adults, 44%; children, 23%) developed a life-threatening opportunistic infection. When analyzed according to the degree of HLA disparity, opportunistic infections occurred in 25% of individuals who were HLA A, B, DRB1 identical, compared with 42% who were HLA class I or class II mismatched. An opportunistic infection occurred in the setting of GVHD in 38% of cases. The probability of developing a life-threatening opportunistic infection was significantly higher in adults after an unrelated transplant compared with children after unrelated BMT ($P = .02$) or adults after related BMT ($P = .02$; Fig 7).

The most common causes of life-threatening opportunistic infection were EBV-LPD ($n = 7$), CMV alone ($n = 5$) or with HHV-6 ($n = 1$), adenovirus alone ($n = 2$) or with CMV ($n = 1$), and toxoplasmosis ($n = 3$). The median time (range) to develop an EBV-LPD after unrelated BMT was 3.4 (2.1 to 6.25) months. EBV-LPD were successfully eradicated in the 5 patients who received donor leukocytes and fatal in the 2 who did not. CMV interstitial pneumonia developed in 5 patients at a median (range) of 2.0 (1.8 to 6.0) months after unrelated BMT and was fatal in all patients. Two patients developed CMV retinitis at 3.5
and 9.0 months despite antiviral therapy. CMV retinitis did not resolve in either patient until donor leukocytes were administered in addition to continued antiviral therapy.

The potentially life-threatening opportunistic infections detailed in this series occurred exclusively in patients whose CD4 cell counts were less than 200 cells/µL (Fig 4) and were fatal in all patients except those receiving donor leukocytes. We examined the relationship between age, T-cell recovery, and risk of life-threatening opportunistic infections. The rate of CD4 recovery was associated with the risk of developing a life-threatening opportunistic infection after an unrelated SBA E- BMT \((P = .07)\). After adjusting for age, the relationship between CD4 reconstitution and the risk of a life-threatening infection was strengthened \((P = .04)\). In addition, we examined the effect of age and risk of opportunistic infections, independent of CD4 recovery. This analysis demonstrated that an adult had a 3.1-fold increased risk of developing a life-threatening opportunistic infection relative to a child \((P = .04; 95\% \text{ confidence interval}, 1.2 \text{ to } 8.5)\). This demonstrates that other factors, in addition to CD4 recovery, contribute to the increased risk of these infections in adult unrelated transplant recipients.

The effects of donor leukocytes administered at doses of 0.2 to 1.0 \(\times 10^6\) CD3\(^+\) T cells/kg (median, 0.5 \(\times 10^6\)/kg) for the treatment of an EBV-LPD are shown in Fig 8. These resulted in the rapid normalization of T-cell numbers in 4 of 5 patients treated for an EBV-LPD, each of whom had CD3\(^+\) T-cell numbers of less than 100 cells/µL immediately before the infusion. Normal numbers of circulating CD8\(^+\) cells were found in each of these 5 patients within 4 weeks of the infusion and CD4 counts greater than 200 cells/µL were achieved in 4 of 5 patients. UPN 1332, the only patient with an EBV-LPD who developed de novo GVHD post-DLI that required systemic steroid therapy, normalized his T-cell numbers within 12 days of DLI infusion, during which time his multiorgan EBV-LPD was eradicated. Although this patient became markedly lymphopenic after initiation of intravenous methylprednisolone, he remains in continuous remission 61+ months post-BMT, off immunosuppressive therapy.

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**Fig 3.** Shown is the recovery of T cells in adults (upper) and children (lower) who were transplanted from HLA A, B, DR\(\beta\) matched (left; ○) versus mismatched (right; ●) unrelated donors. The stippled rectangle denotes the 10th-90th% of 65 normal adults. The horizontal bar represents the median of patients studied within each time period.

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The effect of donor leukocytes at a dose of $0.1 \times 10^6$ CD3$^+$ T cells/kg administered in an effort to prevent EBV-associated lymphoproliferative disorders in 5 EBV-seropositive patients or to eradicate CMV viremia that persisted in 2 patients despite protracted antiviral therapy was less consistent. The increment of CD3$^+$ and CD4$^+$ T cells observed in these 7 patients was smaller and often transient due to the development of GVHD requiring immunosuppressive therapy (data not shown). All 3 patients receiving $0.1 \times 10^6$ donor CD3$^+$ T cells/kg less than 80 days post-transplant developed de novo GVHD post-DLI, compared with none of the 4 individuals who received this cell dose 103 to 157 days post-BMT.

The effect of DLI on antigen-specific responses is shown in 3 CMV-seropositive patients (UPNs 1596, 1630, and 1725) who developed recurrent CMV viremia with (n = 2) or without retinitis (n = 1), despite prolonged antiviral therapy with ganciclovir, foscarnet, and immune globulin. After the infusion of only $0.1 \times 10^6$ kg T cells/kg (n = 2) or $0.5 \times 10^6$ kg T cells (n = 1) from their marrow donors, all 3 patients rapidly developed an anti-CMV proliferative response, cleared their CMV viremia, and remained CMV antigen negative, despite cessation of antiviral therapy (Fig 9). These responses were particularly striking, because the donors had CMV-specific titers of less than 1:10, which is in the range of donors used to provide CMV-negative blood products.

**DISCUSSION**

Although relapse rates are often lower after transplantation of marrow derived from unrelated donors when compared with HLA-matched siblings, DFS is often compromised by a higher incidence of fatal opportunistic infections and GVHD. In the series of 462 recipients of bone marrow derived from unrelated donors facilitated by the NMDP, infection and interstitial pneumonia were the primary and secondary cause of death in greater than 30% of patients, compared with 14% from disease recurrence. In recent reports,
leukemic relapse accounted for 8% to 25% of deaths compared with 38% to 75% from infection.2,9,10,15

Despite this increased risk of infection, only one published study has analyzed parameters of immune reconstitution after unrelated BMT36 and none has correlated them with infection rates. In this report, we have shown that SBA-E- TCD BMT derived from unrelated adult donors are associated with prolonged T-cell lymphopenia and extreme CD4 lymphopenia in adults but not children, that opportunistic infections have occurred only in patients with CD4 cell counts less than 200 cells/µL, and that adoptive immunotherapy with small numbers of unirradiated donor leukocytes can be associated with rapid restoration of CD3+, CD4+, and CD8+ T-cell numbers, antigen-specific T-cell responses, and resolution of CMV- and EBV-associated disease. Comparison of this data with a similar study performed on recipients of HLA-matched sibling BMT20 demonstrates a similar time to engraftment of donor NK cells (1 month) after related and unrelated SBA-E- BMT in both children and adults. No differences were observed in the time to develop normal numbers of circulating CD3+, CD4+, CD45RA+, and CD8+ T lymphocytes in children transplanted with SBA-E- bone marrow derived from unrelated donors when compared with children transplanted from matched sibling donors. However, in contrast to adult recipients of a related SBA-E- BMT who developed normal numbers of CD3+ T cells by 2 to 4 months even when receiving ATG and steroids for graft rejection prophylaxis, adult recipients of unrelated BMT experienced prolonged T lymphopenia, with delayed reconstitution of CD8+ and CD4+ populations, including CD45RA+ CD4+ T lymphocytes.

Several factors could be hypothesized to account for the more profound and prolonged immunologic deficiencies observed among recipients of transplants from unrelated donors. First, major or microvariant HLA disparities between donor and host might, on one hand, alter the capacity of the donor’s lymphoid progenitors to migrate to or mature within the host thymus, or on the other hand, stimulate clinical or subclinical GvHD, thereby further potentiating thymic injury.11,12,21,22 HLA class I microvariant disparities have been detected in up to 48% of unrelated donor-recipient pairs matched by serology for HLA
class I alleles and molecularly matched for DRβ1. Furthermore, increasing evidence suggests that such HLA microvariant disparities may explain, in part, the increased risk of severe GVHD after unmodified matched unrelated marrow grafts when compared with transplants from similarly matched HLA-identical siblings. Although the incidence of grade II-IV GVHD after SBA- E− BMT from unrelated donors is low (17%), it is greater than the 4% incidence of acute grade II
GVHD and absence of grade III-IV GVHD observed in adults transplanted with SBA 'E' matched sibling marrow. In this context, it is possible that mild clinical or even subclinical forms of GVHD could contribute to the extended immunodeficiency observed after unrelated BMT. The significance of microvariant HLA disparities for the redevelopment of T-cell populations may also differ in children versus adults. Thus, in this series, one or two HLA class I or class II microvariant disparities did not appear to affect recovery of T-cell populations or their function in children, but did appear to predispose to more prolonged and profound deficits in adults.

A second factor that likely contributes to the delayed and incomplete immune reconstitution of T cells observed in adults is the involution of the thymus, which normally occurs in adulthood, beginning late in the second decade of life (reviewed in Sprent37). Analysis of immune reconstitution in our patients grouped according to age indicated that, after the first 4 to 6 months posttransplant, there were no significant differences between children who received an unrelated or related SBA 'E' BMT despite administration of ATG and steroids to children receiving unrelated marrow grafts.20 Indeed, the kinetics of reconstitution resembles that recorded in children after autologous or unmodified matched sibling transplants.38 In contrast, adult recipients of SBA 'E' marrow transplants have prolonged states of T-cell cytopenias that are significantly more protracted and severe in the unrelated transplant recipients. The differences in immune reconstitution observed in adults versus pediatric recipients are difficult to ascribe to differences in the lymphoid progenitors or mature lymphocytes administered in the grafts as there were no differences in the adult marrow donor pool used to transplant these two patient groups. This suggests that differences in the host environment, such as the thymus may underlie limitations in immune recovery in adults39,40 and further that genetic disparities between donor and host may affect not only the capacity of mature lymphoid cells to interact with host antigen-presenting cells or host cells infected by viruses, but also the migration of naive cells to the thymus as well as other sites of lymphoid differentiation.

Grade III to IV GVHD can be reduced to less than 10% in children after T10B9-depleted unrelated BMT6-9 and in all patients transplanted with SBA 'E' TCD marrow, even when derived from HLA-mismatched donors. This contrasts with the 20% to 35% incidence of acute grade III-IV GVHD reported after unmodified marrow transplants derived from HLA-A, B
DRβ1 identical unrelated donors, as defined by high resolution molecular typing and the 50% to 70% incidence of severe GVHD recorded when donors who are matched only by serology. Unfortunately, rigorous T-cell depletion to prevent GVHD often requires additional immunosuppression to prevent graft failure, which can increase the risk of opportunistic infections. After related SBA-E BMT, the probability of developing pneumonia secondary to an opportunistic infection increased from 0.10 in patients not receiving ATG and steroids to 0.21 in adults who were. The risk of EBV-LPD has also increased from less than 1% to 8% for patients receiving ATG and steroid to prevent graft failure after a related SBA-E BMT to 11% in recipients of unrelated SBA-E grafts. Although the probability of developing an opportunistic pneumonia was similar in adult recipients of an unrelated and related SBA-E BMT, the fatality rate for these pneumonias in the unrelated group was 100%, compared with 30% in similarly treated recipients of a related BMT.

This group has previously demonstrated a rapid expansion of EBV-specific cytotoxic cells in patients receiving doses of donor leukocytes containing 0.5 to 1.0 × 10⁶ CD3⁺ T cells/kg for the treatment of EBV-LPD after HLA-matched related TCD BMT. As shown in this study, infusions of donor leukocytes transferring as few as 0.2 to 1.0 × 10⁶ CD3⁺ T cells/kg recipient weight regularly induced normalization of CD3⁺, CD4⁺, and CD8⁺ T lymphocyte populations within 18 to 21 days in these unrelated transplant recipients. Striking increases in virus specific immune responses to EBV (Lucas et al data not shown) and to CMV were also detected. These responses were sufficient to induce durable remissions in each of the 5 unrelated transplant recipients with monoclonal EBV-LPD and the 2 patients with CMV-induced retinitis refractory to antiviral therapy. In the latter cases, cessation of viremia was detected in association with recovery of T-cell proliferative responses to CMV antigens. These latter responses are striking in that the donors of the leukocytes themselves had such low titers of CMV-reactive antibody. Although it may be assumed that these donors had low levels of preprimed CMV-specific T cells in their circulation, the rapid recovery of CMV responses in the patients suggests that, in CMV infections as in EBV infections, the numbers of T cells required to induce effective immunity may be small. At this time our data are insufficient to determine whether the increment in T-cell numbers and viral specific responses observed after DLI reflect the presence and/or magnitude of antigenic stimuli (ie, viral load) or the dose of cells infused.

The obvious disadvantage of donor leukocyte infusions is the risk of inciting severe GVHD, particularly in recipients of matched unrelated or HLA-disparate unrelated grafts. In this series, 1 of 7 patients who received donor leukocytes providing....
been detected in murine models. The mechanism responsible for this reduction in GVHD risk late after transplant has also been observed in our analyses of the threshold doses of T cells required to induce GVHD at different times posttransplant. In HLA-matched sibling grafts marrow, T-cell doses exceeding 10^6 T cells/kg are associated with a significant incidence of GVHD when administered in the absence of GVHD prophylaxis. In contrast, when donor leukocytes containing 10^7 T cells/kg patient weight are given greater than 9 to 12 months posttransplant to treat relapsed CML post-SBA-E- BMT, only 2 of 17 patients developed grade II GVHD (MacKinnon et al., Papanicolaou et al., indicating that, late after transplant, higher doses of T cells may be tolerated without risk of GVHD. A similar reduction in GVHD risk late after transplant has also been detected in murine models. The mechanism responsible for these alterations of GVHD risk remain unclear, but may, in part, include the relatively lower sensitivity of host tissues to GVH-induced injury late after myeloablative radiation and chemotherapy, the development of donor T cells from the marrow graft capable of modulating or suppressing the function of alloreactive T cells transferred in the donor leukocyte infusion, or the replacement of host antigen-presenting cells, such as dendritic cells capable of stimulating alloreactive GVH-inducing donor T cells, with donor-derived cells. Although the threshold doses of donor T cells required to induce GVHD are different and often lower than those required for GVHD in HLA-matched recipients, the experience in this small series suggests that doses of 10^6 T cells/kg derived from a matched unrelated donor may be tolerated if administered more than 3 months posttransplant, whereas doses of 0.1 × 10^9/kg may induce significant GVHD if administered earlier in the posttransplant course. If these dose-response relationships are taken into consideration, cautious use of donor leukocytes may be indicated in the treatment of potentially lethal infections due to CMV, EBV, and potentially other viruses (eg, adenovirus), for which other antiviral therapies are either unavailable, ineffective, or, in specific cases, inadequate or intolerable.

Clearly, other approaches for adoptive immunotherapy offer the potential of effectively transferring antiviral immunity without the risk of GVHD, specifically, the use of donor-derived cloned antiviral cytotoxic cells or T-cell lines, such as those used to prevent or treat CMV or EBV-related infections post-BMT. However, this approach is often logistically difficult, generally requiring 7 to 9 weeks for generation. Furthermore, although in vitro propagated cells may provide resistance to one specific viral pathogen, they have little capacity to foster general recovery of the immune system, because they generally include CD8^+ but lack CD4^+ T cells. Infusions of donor leukocytes genetically modified to express a marker for cell selection and a suicide gene (eg, HSV thymidine kinase) can circumvent these obstacles by providing a population of broadly reactive T cells requiring less in vitro generation time, cells that can be eliminated by treatment with ganciclovir in the event that clinically significant GVHD ensues, as shown by Bordignon et al. The success or failure of this latter strategy depends on the sustained expression of transduced genes in the infused cells sufficient to permit the eradication of these cells at any time an untoward GVH reaction develops as well as the inability of the transduced cells to recruit other allogeneic cells that could sustain an acute or chronic GVHD reaction.

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