



Low Incidence of Epstein-Barr Virus–Associated Posttransplantation Lymphoproliferative Disorders in 272 Unrelated-Donor Umbilical Cord Blood Transplant Recipients

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ABSTRACT

Umbilical cord blood (UCB) is being increasingly used for transplantation, but the ability of neonatal T cells to regulate Epstein-Barr virus (EBV)-associated lymphoproliferation is unknown. Because UCB transplantation (UCBT) is associated with a relatively low infused dose of donor T cells, frequent donor-recipient HLA disparity, and use of antithymocyte globulin during conditioning, we hypothesized that the risk of EBV-associated posttransplantation lymphoproliferative disorders (EBV-PTLD) after UCBT may be increased. To investigate the incidence of EBV-PTLD after UCBT, we analyzed 272 unrelated-donor UCBTs performed from August 1993 to December 1999 at Duke University Medical Center and the University of Minnesota. Five cases of EBV-PTLD were identified, with a cumulative incidence of 2% (95% confidence interval, 0.3%-3.7%) at 2 years. EBV-PTLD affected UCB recipients aged 1 to 49 years (median, 8 years), with 4 patients undergoing transplantation for leukemia and 1 for immunodeficiency. Patients received UCB grafts that were HLA matched (n = 1) or mismatched at 1 (n = 1) or 2 (n = 3) HLA loci. Diagnoses occurred at 4 to 14 months (median, 6 months) after UCBT, with 4 of 5 patients having preceding grade II to IV acute graft-versus-host disease and 1 being diagnosed at autopsy. Treatment of 4 patients consisted of withdrawal of immunosuppressive treatment and administration of rituximab, with 2 of 4 patients responding. Thus, the incidence of EBV-PTLD after unrelated-donor UCBT appears similar to that observed after transplantation using unrelated bone marrow (BM) and compares favorably with unrelated-donor T-cell-depleted BM transplantation. Because adoptive immunotherapy with donor lymphocytes is not an available option for recipients of unrelated-donor UCBT, new therapeutic strategies are needed, and rituximab appears promising.

KEY WORDS

Epstein-Barr virus • Lymphoproliferative disorder • Unrelated-donor umbilical cord blood transplantation

INTRODUCTION

Advantages of umbilical cord blood transplantation (UCBT) include rapid availability, tolerance of 0-to-2 HLA-antigen disparity, and potentially decreased rates of severe acute and chronic graft-versus-host disease (GVHD) [1-4]. Although there have been a few reports of Epstein-Barr virus–associated posttransplantation lymphoproliferative disorders (EBV-PTLD) after UCBT [5,6], the risk of this

complication has not been reported. Furthermore, although both innate and stimulated immunity to EBV have been demonstrated in UCB lymphocytes [7-9], the true capacity of naive neonatal T cells to regulate EBV-associated lymphoproliferation is uncertain. To further investigate the risk of EBV-PTLD after UCBT, we reviewed the outcomes of 272 unrelated-donor UCB transplantations performed at the University of Minnesota and Duke University Medical

Center. Herein the clinical features of affected patients and the cumulative incidence of EBV-PTLD are reported.

METHODS

Patients

All patients who had undergone unrelated-donor UCBT at the University of Minnesota (n = 68) and Duke University Medical Center (n = 204) with a minimum of 6 months follow-up were eligible for analysis. Patients underwent transplantation from August 1993 to December 1999, and data analysis was performed as of December 2000. Patients received UCB units with 0 to 3 HLA-A, -B, -DRB1 mismatches obtained from the Placental Blood Programs at the New York Blood Center, the St. Louis Cord Blood Bank, COBLT (Cord Blood Transplantation Study), and through Netcord. Patient diagnoses included acute leukemia, myelodysplasia (MDS), chronic myelogenous leukemia, bone marrow (BM) failure syndromes, immunodeficiency disorders, hemoglobinopathies, and inborn errors of metabolism. For all patients, HLA-A and -B typing was determined by serology, whereas HLA-DRB1 allele-level typing was determined by high-resolution molecular techniques. Treatment protocols were reviewed and approved by the Institutional Review Boards of both institutions and written informed consent was obtained from all subjects or their guardians.

Conditioning and GVHD Prophylaxis

Sixty-one percent of patients were conditioned with a 1320 to 1375 cGy fractionated total body irradiation-based regimen with chemotherapy and 39% with a myeloablative combination chemotherapy-based regimen. Patients with Fanconi anemia received a dose-reduced preparative regimen [10]. All UCB recipients received antithymocyte globulin (ATG), 30 mg/kg per day on days -3 to -1. GVHD prophylaxis consisted of cyclosporine and methylprednisone as previously described [1,2].

EBV-PTLD Diagnosis

Diagnoses were made by biopsies of involved tissues during life in patients 2 to 5 and postmortem in patient 1, with pathological classification according to internationally recognized criteria using routine histology and immunohistochemistry for B-cell markers including CD20, immunoglobulin light chains, and EBV-associated antigens [11]. Additional flow cytometry for lineage and clonality analysis, molecular studies for immunoglobulin heavy-chain gene rearrangement, EBV genome, and restriction-fragment length polymorphisms were performed on patient biopsy specimens from patients 2 and 3 [11]. The diagnosis of EBV-PTLD in patients 4 and 5 was supported by detection of diagnostic levels of the EBV genome in the peripheral blood using semiquantitative polymerase chain reaction methodology as per McDiarmid et al. [12], with unique primers developed by Memorial Sloan Kettering Cancer Center used for patient 5 (V. Prasad, oral communication, April 2001).

Statistical Analysis

The estimate of EBV-PTLD was expressed as a cumulative incidence [13]. Death without EBV-PTLD was treated as a competing risk.

RESULTS

Five cases (Minnesota, n = 3; Duke, n = 2) of EBV-PTLD were identified for a cumulative incidence of 2% (95% confidence interval, 0.3%-3.7%) at 2 years. EBV-PTLD affected UCB recipients aged 1 to 49 years (median, 8 years), with 4 patients receiving transplants for leukemia/ advanced MDS and 1 for congenital immunodeficiency. Patients received UCB grafts, which were HLA matched (n = 1) or mismatched at 1 (n = 1) or 2 (n = 3) HLA loci, after a number of different conditioning regimens, all of which contained ATG. Each patient achieved myeloid engraftment prior to day 35 with complete donor chimerism and no evidence of recurrent disease. All patients were undergoing treatment for GVHD when EBV-PTLD developed (3 for acute GVHD and 2 for chronic GVHD preceded by acute). Therapy for GVHD consisted of either cyclosporine or FK506 (tacrolimus) and corticosteroids in 4 patients, with 1 patient receiving multiple immunosuppressant therapies (Table 1).

The characteristics of the EBV-PTLD are summarized in Table 2. Diagnosis of EBV-PTLD occurred at 4 to 14 months (median, 6 months) after UCBT, with 1 patient being diagnosed at autopsy. Four of 5 patients had disseminated disease. EBV-PTLD pathology varied from polymorphic (n = 4) to monomorphic (n = 1), with all cases being positive for B-cell markers including CD20. The diagnosis of EBV-PTLD, made by clinical manifestations and biopsy of involved tissue, was further supported by very high copy numbers of the EBV genome in 2 patients (patients 4 and 5) [14-18]. The malignant tissue was clonal and of donor origin in 2 of 2 patients tested (patients 2 and 3).

Treatment of 4 patients consisted of reduction in immunosuppression and intravenous (IV) rituximab, 375 mg/m² per dose weekly for 1 to 3 doses. Patient 2 received additional therapy with acyclovir, 10 mg/kg IV every 8 hours; α -interferon 1,000,000 U/d subcutaneously for 3 days (withdrawn due to rapidly progressing pancytopenia); and cytotoxic chemotherapy (vincristine, 2 mg IV, and methylprednisolone, 1 g IV, on day 7; adriamycin, 25 mg/m² IV, cyclophosphamide, 750 mg/m², and vincristine, 1.5 mg IV, on day 12; and methylprednisolone, 200 mg/d, on days 12-16) without response. Two of 4 patients responded to therapy at a median follow-up of 14 months, whereas 2 failed to demonstrate significant response despite being CD20 positive. These 2 patients died of EBV-PTLD and sepsis/organ failure.

DISCUSSION

PTLD, usually of B-cell origin, can manifest as a wide spectrum of abnormal lymphoid proliferation, from polyclonal reactive hyperplasia to polymorphic PTLD to monomorphic lymphoma, usually of the diffuse large cell type [11]. It is well established that infection with EBV plays a major role in PTLD etiology, and direct incorporation of the EBV genome into the abnormal lymphoid tissue can often be demonstrated. This herpes-group virus infects 95% of the population by adulthood, with latent virus persisting within B lymphocytes. It is proposed that immunosuppression, particularly defective cytotoxic T-cell function, permits EBV reactivation and the uncontrolled proliferation of EBV-driven B cells [16].

Table 1. Clinical Characteristics of Unrelated-Donor UCBT Recipients with EBV-PTLD*

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age, y	7	49	49	8	1
Diagnosis	Relapsed AML (prior autoBMT)	Accelerated- phase CML	Advanced MDS	Secondary AML	Wiskott-Aldrich syndrome
Nucleated cell dose†	2.9×10^7	1.2×10^7	1.6×10^7	4.1×10^7	8.9×10^7
T-cell dose‡	4.2×10^6	2.1×10^6	1.4×10^6	3.6×10^6	6.4×10^6
HLA match	6/6	5/6	4/6	4/6	4/6
Conditioning	TBI 1320 cGy, Cy 120 mg/kg, ATG	TBI 1320 cGy, Cy 120 mg/kg, ATG	TBI 1320 cGy, Cy 120 mg/kg, ATG	TBI 1250 cGy, Mel 135mg/m ² , ATG	Bu 480 mg/m ² , Cy 200 mg/kg, ATG
GVHD type (grade)	Acute: skin (II)/chronic	Acute: skin, upper gut (II)	Acute: upper gut (II)	Acute: skin (I)	Acute: skin, liver(IV)/chronic
GVHD therapy	CSA/steroids	CSA/steroids	CSA/steroids	FK506/steroids	FK506/steroids/ dacluzimab/ azathioprine

*UCBT indicates umbilical cord blood transplant; EBV-PTLD, Epstein-Barr virus-associated posttransplantation lymphoproliferative disorder; AML, acute myeloid leukemia; auto-BMT, autologous bone marrow transplantation; CML, chronic myelogenous leukemia; MDS, myelodysplasia; TBI, total body irradiation; Cy, cyclophosphamide; ATG, antithymocyte globulin; Mel, melphalan; Bu, busulphan; GVHD, graft-versus-host disease; CSA, cyclosporine A; steroids, corticosteroids; FK506, tacrolimus.

†Cryopreserved cell dose per kilogram recipient body weight.

‡Infused cell dose per kilogram recipient body weight.

PTLD after BM transplantation (BMT) is usually a rapidly lethal complication, occurring predominantly in the first 6 months [19]. A review of 18,014 allogeneic BMT patients by Curtis et al. reported a cumulative PTLD incidence of 1% at 10 years [19], whereas 2% of allogeneic BMT cases were complicated by PTLD in a Minnesota series [20]. A review by the National Marrow Donor Program of the outcomes of 5075 recipients of unrelated-donor BMTs who received GVHD prophylaxis with either

immunosuppressive therapy alone (n = 3785) or T-cell depletion (TCD) of donor BM (n = 1290) revealed a 2-year incidence of EBV-PTLD of 1% ± 1% with immunosuppression compared to a 6% ± 2% incidence in recipients of TCD BMTs [21].

In the review by Curtis et al., risk factors strongly associated with PTLD after BMT were unrelated donor or ≥2 HLA-mismatched related donor, TCD of donor BM, and use of ATG or anti-CD3 antibody for prophylaxis/treat-

Table 2. Characteristics of EBV-PTLD in Unrelated-Donor UCBT Recipients*

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Diagnosis†	14 mo	4 mo	5 mo	6 mo	9 mo
Pathology	Polymorphous B cell/EBV ⁺ Clonality: NA	Monomorphic B cell/EBV ⁺ Monoclonal Origin: donor	Polymorphous B cell/EBV ⁺ Monoclonal Origin: donor	Polymorphous B cell/EBV ⁺ Clonality: NA PB EBV ^{+++‡}	Polymorphous B cell/EBV ⁺ Clonality: NA PB EBV ^{+++‡}
Sites of disease	LA: chest, abdomen Lungs Abdo organs	Widespread LA Upper gut Spleen	Stomach Single abdo LN	LA: neck, chest Lungs	Widespread LA Gut Lungs
Therapy	None (diagnosis at autopsy)	Acyclovir/α-IFN, reduced IS, rituximab (3)§, chemotherapy	Reduced IS, rituximab (2)§	Reduced IS, rituximab (1)§	Reduced IS, rituximab (2)§
Outcome	Death due to: GVHD, infection, EBV-PTLD	Death due to: pneumonitis (idiopathic), EBV-PTLD	Remission (follow-up: 13 mo)	Remission (follow-up: 15 mo)	Death due to: GVHD, infection, EBV-PTLD

*EBV-PTLD indicates Epstein-Barr virus-associated posttransplantation lymphoproliferative disorder; UCBT, umbilical cord blood transplant; NA, not available; PB, peripheral blood; LA, lymphadenopathy; abdo, abdominal; LN, lymph node; IFN, interferon; IS, immunosuppression; GVHD, graft-versus-host disease.

†Time from UCBT to EBV-PTLD diagnosis.

‡Polymerase chain reaction for EBV DNA performed on PB.

§Rituximab given at 375 mg/m². Number in parentheses indicates number of doses given at weekly intervals.

ment of acute GVHD. A weaker association with grades II to IV acute GVHD was found, although extensive chronic GVHD acted as a risk factor for late-onset EBV-PTLD [19]. The risk associated with TCD of HLA-mismatched related or HLA-matched unrelated donors is supported by the high cumulative EBV-PTLD incidences of 5% to 25% in recipients of such transplants [22]. The other series have found TCD, transplantation for immunodeficiency, and donor age to be the most significant risk factors [20,21].

Application of these risk factors after BMT to unrelated-donor UCBT may predict an increased risk of EBV-PTLD in UCBT due to the relatively low donor T-cell dose, frequent donor-recipient HLA disparity, and use of ATG during conditioning. Conversely, a potential advantage may be that nearly all neonatal donors are EBV negative, thus reducing the risk from transfer of EBV-infected lymphocytes within the graft [23]. Also, UCBT recipients may be at an advantage by virtue of a relatively reduced likelihood of severe acute and extensive chronic GVHD [1-4].

Fortunately, this series does not suggest a greatly increased incidence of EBV-PTLD after unrelated-donor UCBT. In fact, the incidence compares favorably with the incidences reported after unrelated-donor BMT with TCD [21,22]. Because 1 patient had EBV-PTLD detected at autopsy, it is always possible that other cases have remained undiagnosed. However, this issue applies equally to the estimated incidence after transplantation with other sources. Also, the 2 centers in this study practice close long-term follow-up of their patients, facilitating diagnosis of complications even if late in the posttransplantation course. It is notable that 4 of the 5 UCBT patients developed EBV-PTLD in the context of grades II to IV acute GVHD, with all patients on immunosuppression at disease onset and the 2 patients with relatively late-onset disease both having chronic GVHD.

How immune recovery after UCBT compares with that after transplantation of hematopoietic stem cells from other sources is only just beginning to be investigated. Thomson et al. reported a numerical recovery of T cells at 9 to 12 months, of B cells at 6 months, and of natural killer (NK) cells at 2 months after transplantation [24]. Although the recovery of CD8⁺ T cells was thought to be delayed compared with that seen after transplantation with other sources of hematopoietic stem cells, no difference in functional immune recovery was documented. Weinberg et al. have shown that UCBT recipients have no evidence of decreased T-cell receptor excision circles, despite continuation of immunosuppressive drugs [25]. In regard to EBV-specific immunity, Marshall et al. reported undetectable EBV-specific T cells in 4 UCBT recipients [26]. However, EBV viral titers were not elevated in these patients. Furthermore, Moretta et al. have shown that the innate immunity against EBV in UCB is in fact mediated by CD4⁺ and NK cells [7]. Also, Early et al. have demonstrated more rapid transformation of naive CD4⁺ T cells to effector cells in newborns than adults, which may counteract diminished primary T-cell responses [27]. Finally, EBV-specific immune effectors may be induced in vitro [8,9], and in vivo correlates of such events may mediate EBV-specific immunity in the UCBT recipient.

Adoptive immunotherapy with donor leukocytes has been cited by some as the most effective therapy for BMT-

associated EBV-PTLD. In 1994, Papadopoulos et al. reported use of unmanipulated leukocytes from the original EBV-seropositive donors [28]. To avoid GVHD, Heslop et al. have generated EBV-specific cytotoxic T lymphocytes and have demonstrated their efficacy in both prophylaxis and therapy of EBV-PTLD [29]. However, unrelated-donor UCBT precludes therapy with donor leukocytes unless T cells are removed from the graft preinfusion. Although ex vivo expansion of UCB T cells is being investigated [30], other treatment strategies are needed.

The most promising new alternative therapy for EBV-PTLD is the anti-CD20 chimeric monoclonal antibody rituximab [31]. Kuehnle et al. recently described successful rituximab therapy of EBV-PTLD in 3 BMT patients [17]. Milpied et al. have documented complete remission in 5 of 6 BMT patients after rituximab therapy in a retrospective study, with prolonged survival in 4 patients [32]. Therefore, rituximab, combined with reduction in immunosuppression if applicable, may be a successful therapy for some UCBT patients as suggested by the response in 2 of 4 patients in this report. Prognostic factors for the treatment of EBV-PTLD with murine anti-B-cell monoclonal antibodies have been described [33], but such information is not currently known for rituximab.

McGuirk et al. reported use of irradiated haploidentical donor lymphocytes in combination with rituximab to control EBV-PTLD after haploidentical BMT with TCD [34]. The relative value of each of these therapies in this case is unclear, although allogeneic leukocytes have been used as therapy for solid organ-associated PTLT [35]. Therefore, an experimental approach to therapy for UCBT patients not responding to rituximab alone could be irradiated lymphocytes from alternative adult EBV-seropositive donors and rituximab. Another potential approach would be preemptive therapy with rituximab in those patients demonstrating high levels of the EBV genome in the peripheral blood prior to the onset of clinical manifestations of disease [18]. Greater experience is required to determine if this use of rituximab will be warranted on a cost-benefit basis, but such treatment could be a consideration in unrelated-donor UCBT patients with GVHD.

In summary, the incidence of EBV-PTLD after unrelated-donor UCBT appears similar to that seen after transplantation of allogeneic hematopoietic stem cells from other sources and compares favorably with the incidence of EBV-PTLD reported after unrelated-donor BMT with TCD. For those UCBT patients who do develop this complication, new attention should be directed toward developing alternative treatment strategies.

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