Biology of Blood and Marrow Transplantation 13:665-674 (2007)

1083-8791/07/1306-0001$32.00/0
doi:10.1016/j.bbmt.2007.01.082

Outcomes of Unrelated Umbilical Cord Blood Transplantation for X-Linked Adrenoleukodystrophy

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Received August 18, 2006; accepted January 26, 2007

ABSTRACT

Adrenoleukodystrophy (ALD) is an X-linked disorder caused by a defect in the metabolism of long chain fatty acids leading to demyelination, neurodegeneration, and death. The disease typically presents in young boys and adolescent boys. Allogeneic bone marrow transplantation has been used to halt progression of the disease. However, many patients lack suitable HLA- matched related donors and must rely on unmatched donors for a source of stem cells. The purpose of this study was to evaluate outcomes of unrelated donor umbilical cord blood transplantation after chemotherapy-based myeloablative conditioning and retrospectively determine if baseline studies correlate and help predict outcome. Between November 22, 1996, and November 3, 2005, 12 boys with X-linked ALD who lacked HL- matched related donors were referred to Duke University Medical Center for transplantation. These children were conditioned with myeloablative therapy including busulfan, cyclophosphamide, and antithymocyte globulin before receiving umbilical cord-blood transplants from unrelated donors. Baseline studies of neurophysiologic, neuroimaging, and neurodevelopmental status were performed and patients were subsequently evaluated for survival, engraftment, graft-versus-host disease, and neurodevelopmental outcomes. A substudy evaluated whether baseline neuroimaging and neurophysiologic studies correlated with cognitive and motor function and if these studies were predictive of posttransplantation outcomes. The umbilical cord blood grafts had normal levels of very long chain fatty acids. They delivered a median of 6.98×10^7 nucleated cells per kilogram of recipient body weight and were discordant for up to 4 of 6 HLA markers. Neutrophil engraftment occurred at a median of 22.9 days after transplantation. Three patients had grade II-IV acute graft-versus-host disease; 2 had extensive chronic graft-versus-host disease. Cumulative incidence of overall survival of the group at 6 months is 66.7% (95% confidence interval 39.9-93.3%). Median follow-up was 3.3 years (range 12 days to 6.3 years). As previously reported with bone marrow transplantation, symptomatic patients faired poorly with lower survival and rapid deterioration of neurologic function. This study included 3 patients transplanted at a very young age (2.6-3.5 years) before the onset of clinical symptoms who continue to develop at a normal rate for 3-5 years posttransplant. Although baseline Loes scores correlated with cognitive and motor outcome, neurophysiologic studies failed to show statistically significant differences. Transplantation of boys with X-linked ALD using partial HLA-matched umbilical cord blood yields similar results to those previously reported after bone marrow transplantation. Superior outcomes were seen in neurologically asymptomatic boys less than 3.5 years of age at the time of transplantation. Baseline Loes scores were a strong predictor of cognitive and motor outcome.

KEY WORDS

Umbilical cord blood transplantation • Neurodevelopmental outcomes • Adrenoleukodystrophy

INTRODUCTION

Adrenoleukodystrophy is an X-linked disorder (X-ALD) caused by the deficiency of the ABCD1 gene that encodes for a peroxisomal protein membrane. It is associated with the accumulation of very long chain fatty acids (VLCFA) that can be measured in the plasma for diagnosis. X-ALD affects the testes, adrenal cortex, and the nervous system. The cerebral form leads to demyelination and typically affects young boys who present with behavioral lability, visual impairment, seizures, progressive loss of cognitive and motor function, and death by 10 years of age [1-3]. A milder adult form referred to as adrenomyeloneuropathy involves mainly the spinal cord. Hematopoietic stem cell transplantation (HSCT) arrests progression of cerebral X-ALD and other leukodystrophies in patients with early stages of disease [4-7]. However, many patients cannot identify an appropriately matched sibling or unrelated adult donor [4,6,7]. Unrelated donor umbilical cord blood (UCB) has been shown to successfully reconstitute marrow in children following allogeneic transplant for malignant and nonmalignant diseases [8-10]. We now report the outcomes after UCB transplantation in a series of 12 boys with X-ALD. We also correlate baseline neurodevelopmental, neurophysiologic, and brain imaging findings with functional outcomes.

METHODS

Between November 22, 1996, and November 3, 2005, 12 boys with adrenoleukodystrophy lacking HLA-matched related donors were referred to the Pediatric Bone Marrow Transplant Program at Duke University. All patients were evaluated with a baseline brain MRI, peripheral nerve conduction velocity (NCV), brainstem auditory evoked responses (BAER), visual evoked potentials (VEP), electroencephalogram (EEG), and neurodevelopmental evaluations. The diagnosis of ALD was confirmed by the presence of abnormally high levels of long chain fatty acids (LCFA) in the blood measured by capillary gas chromatography of pentafluorobenzyl bromide fatty acid esters [11]. After parental informed consent was obtained, 4 patients were enrolled in the Cord Blood Transplantation Study (COBLT), 4 patients enrolled on the COBLT-Extended Access Protocol (COBLT-EAP), and 4 patients were enrolled in an ongoing single-institution study. All were approved by the institutional review board at Duke University Hospital. The transplant related outcomes of 8 patients transplanted on the COBLT or the COBLT-EAP studies were previously reported as part of a larger cohort of patients with lysosomal storage diseases. These included survival, engraftment, and graft-versus-host-disease (GVHD) [10]. Neurophysiologic, neuroimaging, or neurodevelopmental outcomes were not previously reported in any of the patients.

Selection of Donors

Cord blood units from unrelated donors were selected from public cord blood banks listing units through the National Marrow Donor Program or the New York Blood Center after a search using intermediate resolution HLA typing for class I (A and B) and high-resolution typing of HLA-DRB1. The units with the highest number of nucleated cells (minimum, 3×10^7 per kilogram of body weight) matching at least 4 of 6 HLA loci were selected and tested for normal levels of LCFA [11]. Cell dosing was prioritized over HLA matching for unit selection for transplantation. Final unit selection was based on highest cell dose with closest HLA match and normal very long chain fatty acids (VLCFA) levels.

Conditioning Regimen

Patients underwent a myeloablative preparative regimen of busulfan, cyclophosphamide, and antithymocyte globulin as previously described [12-14]. First-dose pharmacokinetic studies were performed during busulfan therapy targeting a steady-state concentration (Css) of 600-900 ng/mL. Patients received phenytoin prophylaxis against seizures during therapy with busulfan; mesna was administered during cyclophosphamide therapy for prophylaxis against hemorrhagic cystitis.

Transplantation Procedure

Cryopreserved units of cord blood were thawed and processed as previously reported [15]. Thawed units were tested for total number of nucleated cells, clonal hematopoietic progenitor cells, $CD3^+$, $CD34^+$ cells, ABO, and Rh typing, cell viability, and sterility.

Prophylaxis against and Treatment of GVHD

The patients received cyclosporine for 9 months and methylprednisolone for 2 to 3 months as prophylaxis against GVHD. In the absence of chronic GVHD (cGVHD), immune suppression was discontinued approximately 1 year posttransplant [10,12,13]. The severity of acute GVHD (aGVHD) was scored using standard criteria [16]. Acute grade 1 GVHD of the skin was treated with topical creams, an escalation in methylprednisolone, or both. Patients with moderate to severe GVHD received pulsed doses of methylprednisolone 500 mg per square meter given intravenously every 12 hours for 4 total doses before GVHD treatment was changed from cyclosporine to tacrolimus, alone or in combination with daclizumab.