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# A Reduced-Toxicity Regimen Is Associated with Durable Engraftment and Clinical Cure of Nonmalignant Genetic Diseases among Children Undergoing Blood and Marrow Transplantation with an HLA-Matched Related Donor

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A B S T R A C T

Blood and marrow transplantation (BMT) is a standard curative therapy for patients with nonmalignant genetic diseases. Myeloablative conditioning has been associated with significant regimen-related toxicity (RRT), whereas reduced-intensity conditioning regimens have been associated with graft failure. In this prospective pilot trial conducted at 2 centers between 2006 and 2013, we report the outcome of 22 patients with nonmalignant genetic diseases who were conditioned with a novel reduced-toxicity regimen: i.v. busulfan (16 mg/kg), alemtuzumab (52 mg/m$^2$), fludarabine (140 mg/m$^2$), and cyclophosphamide (105 mg/kg). The median age of the study population was 3.5 years (range, 5 months to 26 years). No cases of sinusoidal obstruction syndrome, severe or chronic graft-versus-host disease (GVHD), or primary graft failure were reported. Median time to neutrophil engraftment (>500 cells/μL) and platelet engraftment (>20K cells/μL) were 19 (range, 12 to 50) and 23.5 (range, 14 to 134) days, respectively. The median length of follow-up was 3 years (range, .2 to 6.3). The overall survival rates were 95% at 100 days (95% confidence interval, .72 to .99) and 90% at 6 years (95% confidence interval, .68 to .98). RRT and chronic GVHD are significant barriers to BMT for patients with nonmalignant genetic diseases. This alemtuzumab-based reduced-toxicity regimen appears to be promising with durable engraftment, effective cure of clinical disease, low rates of RRT, and no observed chronic GVHD.



## INTRODUCTION

For many patients with nonmalignant genetic diseases, the decision burden regarding the immediate risks of blood and marrow transplantation (BMT) versus continuation of noncurative therapy often leads to delays in BMT. Unfortunately, many of these patients present for BMT after they have more advanced symptoms of their clinical disease, and such delays may be associated with poorer outcomes [1].

BMT with a histocompatible-related donor after standard myeloablative conditioning (MAC) has been associated with significant regimen-related toxicity (RRT) [2-5]. The nonmalignant genetic conditions represent a heterogeneous group of diseases with varying rates of RRT. These toxicities include noninfectious pulmonary toxicity and sinusoidal obstructive syndrome among patients with hemophagocytic lymphohistiocytosis, a high rate of grade ≥II graft-versus-host disease (GVHD) among patients with hemoglobinopathies, and a 9% graft failure rate among patients with thalassemia [6-8]. Interestingly, 30% of patients who received matched sibling donor BMT for Hurler syndrome developed mixed chimerism, despite the use of MAC, suggesting that sustained hematopoietic engraftment may pose a challenge among some metabolic disorders [9]. An

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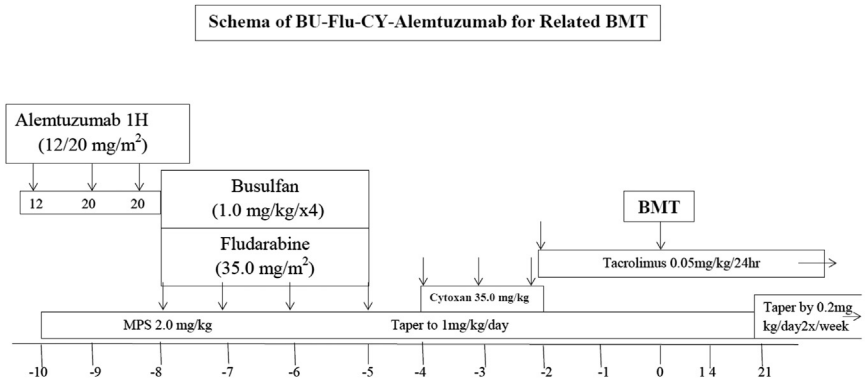


**Figure 1.** Schematic diagram of the treatment regimen. The conditioning regimen consisted of i.v. fludarabine (140 mg/m$^2$), i.v. busulfan (16 mg/kg; with pharmacokinetic dose adjustments to achieve overall target concentration steady state of 800 to 1000 ng/mL), alemtuzumab (52 mg/m$^2$), and cyclophosphamide (105 mg/kg). Either tacrolimus or cyclosporine was initiated on day −2 and continued for a minimum of 1 year post-transplant. Methylprednisolone (MPS) was tapered with a goal of discontinuation by day +35.

effective conditioning strategy for patients receiving related BMT for nonmalignant genetic diseases must be associated with low rates of RRT while remaining sufficiently immunoablative to allow for adequate levels of sustained donor chimerism.

Although RRT associated with standard MAC regimens (such as with busulfan, cyclophosphamide, and antithymocyte globulin [ATG]) may be acceptable for patients with leukemia whose disease may be immediately life threatening, this is a major obstacle to the application of curative BMT to nonmalignant genetic diseases. Reduction of the cyclophosphamide dose may expose patients to an increased risk of graft rejection, unless additional immunoablative drugs are added to the regimen. In 2004, Sodeni et al. [10] reported improved outcomes associated with dose reduction of cyclophosphamide and the addition of other agents to achieve adequate immunosuppression. Bernaudin et al. [11] showed that the addition of ATG to MAC regimens reduced the rejection rate among hematopoietic stem cell transplantation recipients with sickle cell disease from 22.6% to 3%. In the same year, we reported that the use of alemtuzumab (a monoclonal antibody that binds to CD52 on mature lymphocytes) was associated with reduced RRT, such as severe GVHD [12]. We hypothesized that among patients with nonmalignant genetic diseases receiving a matched related donor BMT, the addition of alemtuzumab to a regimen of busulfan, fludarabine, and a reduced dose of cyclophosphamide would maintain adequate immune suppression, allow acceptable rates of sustained donor engraftment, and allow low rates of RRT and chronic GVHD.

## METHODS

This prospective pilot study was approved by the institutional review boards at Children's Hospital Los Angeles and Stanford Lucile Packard Children's Hospital. Informed consent was obtained in accordance with the Declaration of Helsinki.

### *Patients*

Patients with nonmalignant genetic diseases who were candidates for allogeneic transplantation at either institution between 2006 and 2013 and had a 10/10 or 9/10 allele matched histocompatible sibling or related donor were eligible for this study protocol. Subjects must have had adequate physical and vital organ function, as measured by the following: (1) cardiac shortening fraction >26% or left ventricular ejection fraction at rest >40%; (2) bilirubin, alanine aminotransferase, and aspartate aminotransferase less than 3 times the upper limit of normal (as per local laboratory) for age (with the exception of isolated hyperbilirubinemia due to Gilbert syndrome); (3) serum creatinine less than 2 times the upper limit of normal for age or creatinine clearance or glomerular filtration rate >50% lower limit of normal for age; and (4) forced expiratory volume in 1 second, forced vital capacity, and diffusing capacity of lung for carbon monoxide (corrected for hemoglobin) >50% predicted or pulse oximetry oxygen saturation >92% on room air. Patients with Karnofsky performance status <70% or Lansky <40%; uncontrolled bacterial, viral, or fungal infections; seropositivity for HIV; acute active hepatitis; diagnosis of end-organ dysfunction; or diagnosis of severe combined immunodeficiency and Fanconi anemia were excluded.

### *Preparative Regimen*

The conditioning regimen (Figure 1) consisted of i.v. fludarabine at a total dose of 140 mg/m$^2$, i.v. busulfan at a total dose of 1 mg/kg/dose for 16 doses (with pharmacokinetic dose adjustments after dose 1 and then doses 5 and 7 if adjustments were made) to achieve an overall target concentration steady state of 800 to 1000 ng/mL, alemtuzumab (Campath 1H, Genzyme Corporation, Cambridge, MA) at a total dose of 52 mg/m$^2$, and cyclophosphamide at a total dose of 105 mg/kg. Mesna was administered per standard operating procedure at each institution.

### *GVHD Prophylaxis*

GVHD prophylaxis (Figure 1) consisted of a calcineurin inhibitor and methylprednisolone. Either tacrolimus or cyclosporine was initiated on day −2 and titrated to maintain a serum trough level of approximately 7 to 10 ng/dL for tacrolimus or 200 to 300 ng/dL for cyclosporine. The drug was continued for a minimum of 1 year post-transplant. Methylprednisolone was administered at 2 mg/kg/day in divided doses at the start of the conditioning regimen during the alemtuzumab infusion until day +3. Subsequently, methylprednisolone was tapered with a goal of discontinuation by day +35.

### *Graft Source*

Histocompatible bone marrow donors 10/10 or 9/10 allele-matched were the main graft source on this protocol. One patient received a combination of umbilical cord and marrow products from the same related donor. The marrow was manipulated only for red blood cell or plasma removal per standard institutional practice in event of an ABO-mismatch between the donor and recipient.

### *Supportive Care*

All patients remained hospitalized in protective isolation until there was evidence of engraftment of donor cells and sufficient clinical recovery. Viral prophylaxis consisted of i.v. acyclovir (1500 mg/m$^2$/day) until day +30 post-BMT. If the donor or recipient were positive for cytomegalovirus (CMV) serology, CMV PCR assays were sent at a minimum of weekly until day +100 post-BMT. If patients developed CMV viremia, ganciclovir (5 mg/kg) was administered intravenously twice daily. *Pneumocystis carinii* pneumonia prophylaxis consisted of oral trimethoprim-sulfamethoxazole 75 mg/m$^2$ or 2.5 mg/kg trimethoprim twice daily from admission until day −2 post-BMT. *Pneumocystis carinii* pneumonia prophylaxis was resumed after count recovery, per institutional practice. Standard antifungal prophylaxis consisted of fluconazole orally or intravenously 5 mg/kg until at least day +100 post-BMT. Standard antiseizure prophylaxis was administered. Patients with sickle cell disease continued antiseizure prophylaxis until discontinuation of calcineurin inhibitors.