Excellent survival after sibling or unrelated donor stem cell transplantation for chronic granulomatous disease

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Background: Matched related donor (MRD) hematopoietic stem cell transplantation (HSCT) is a successful treatment for chronic granulomatous disease (CGD), but the safety and efficacy of HSCT from unrelated donors is less certain.
Objective: We evaluated the outcomes and overall survival in patients with CGD after HSCT.
Methods: We report the outcomes for 11 children undergoing HSCT from an MRD (n = 4) or an HLA-matched unrelated donor (MUD) (n = 7); 9 children were boys, and the median age was 3.8 years (range, 1-13 years). We treated both X-linked (n = 9) and autosomal recessive (n = 2) disease. Nine children had serious clinical infections before transplantation. The conditioning regimens contained busulfan, cyclophosphamide, cytarabine, or fludarabine according to the donor used. All patients received alemtuzumab (anti-CD52 antibody). Additional graft-versus-host disease (GvHD) prophylaxis included cyclosporine and methotrexate for MUD recipients and cyclosporine and prednisone for MRD recipients.
Results: Neutrophil recovery took a median of 16 days (range, 12-40 days) and 18 days (range, 13-24 days) for MRD and MUD recipients, respectively. Full donor neutrophil engraftment occurred in 9 patients, and 2 had stable mixed chimerism; all patients had sustained correction of neutrophil oxidative burst defect. Four patients had grade I skin acute GVHD responding to topical treatment. No patient had grade II to IV acute GvHD or chronic GvHD. All patients are alive between 1 and 8 years after HSCT.
Conclusion: For CGD, equivalent outcomes can be obtained with MRD or MUD stem cells, and HSCT should be considered an early treatment option. (J Allergy Clin Immunol 2012;129:176-83.)

Key words: *Chronic granulomatous disease, primary immunodeficiencies, bone marrow transplantation, graft-versus-host disease*

Abbreviations used
CGD: Chronic granulomatous disease
ConA: Concanavalin A
GvHD: Graft-versus-host disease
HSCT: Hematopoietic stem cell transplantation
MRD: Matched related donor
MUD: Matched unrelated donor
SI: Stimulation index

Chronic granulomatous disease (CGD) is an inherited immunodeficiency estimated to occur in one in 250,000 persons.[1] The disease is caused by mutations in any of the genes that encode the proteins of the phagocytic nicotinamide adenine dinucleotide phosphate oxidase enzyme complex ($gp91^{phox}$, $p47^{phox}$, $p67^{phox}$ $p22^{phox}$, and $p40^{phox}$).[2] The disease is X-linked in 65% of affected subjects ($gp91^{phox}$) and autosomal recessive in others. Defects in this enzyme complex render neutrophils incapable of phagocytic microbial killing, leading to severe and recurrent infections. Patients with CGD have an impaired quality of life with frequent hospitalizations, recurrent diarrhea, infections, and inflammatory organ damage.[3] Furthermore, established infections (fungal and bacterial organisms, including *Staphylococcus aureus*, *Burkholderia cepacia*, and *Aspergillus fumigatus*) are difficult to eradicate and remain a significant cause of mortality.

In a large European study of more than 400 patients with CGD followed over 50 years, the mean age at death for patients with X-linked CGD was 38 years.[1] Other reports suggest a life expectancy of 25 to 30 years for patients with X-linked CGD patients.[4] The annual rate of death from CGD in the United

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States is 2% to 5%, and only 50% of the patients will survive to 30 years of age.[5,6]

The standard of care for CGD includes infection prophylaxis with antibiotics, antifungal agents and IFN-γ.[7-9] Gallin et al[10] have shown that itraconazole prophylaxis therapy has been widely used and proved to be safe and effective in children and adults with CGD to prevent fungal infections. Despite these measures, morbidity remains significant in patients with CGD. Patients can have drug-associated toxicity and suboptimal compliance, especially among adolescents and young adults, compromising the efficacy of prophylaxis measures. For these reasons, there is a need for better and definitive therapies.

The optimal treatment for most patients with severe primary immunodeficiencies is hematopoietic stem cell transplantation (HSCT) from an HLA-matched related donor (MRD).[11] Unfortunately, such donors are available for only a minority of patients. Matched unrelated donor (MUD) HSCT has been successfully used for other primary immunodeficiencies and phagocytic disorders (including leukocyte adhesion defect), with an overall survival of approximately 80%.[12-14] Unfortunately, these studies have also shown a high incidence of graft-versus-host disease (GvHD).[12-14]

Because most children with CGD lack a related donor, Soncini et al[15] described the European experience in a 10-patient CGD cohort who received stem cells from an HLA-MUD. They reported an overall survival of 90%, with a 30% incidence of grade II acute GvHD and 1 patient having chronic GvHD. In this cohort 1 patient had graft failure and required a second transplantation.[15] Recent data from the European consortium (SCETIDE) described a total of 41 patients with CGD undergoing transplantation with an overall survival of 81% at 5 years; the deaths occurred early in the first 6 months after transplantation (verbal communication kindly given by Paul Landais and Nizar Mahlaoui, September 8, 2011). An unpublished survey of North American centers treating patients with CGD found that 59 patients had undergone allogeneic transplantation with a 71% survival outcome.[2] We now report our single US-center experience of treating 11 patients with CGD with HLA-MRD and MUD transplants.

METHODS

Patients

Eleven patients with CGD and a history of significant morbidity with HLA-matched stem cell donors were eligible for HSCT according to a study approved by our institutional review board (Table I). CGD was confirmed by the absence of oxidase activity in neutrophils, which was determined by means of dihydrorhodamine oxidation analysis in all patients. Nine of these patients had X-linked CGD (determined by means of identification of a carrier mother, $gp91^{phox}$ mutation analysis, or both), 1 girl had autosomal recessive CGD ($p67^{phox}$), and a mutation could not be identified for 1 girl (Table I). Likewise, mutations could not be identified for 3 boys but are likely *CYBB* mutations because maternal oxidative burst studies suggested a carrier state for this mutation. Irrespective of the genetic mutations, all patients had very low stimulation indices (SIs) at diagnosis, which is suggestive of high-risk disease.[2]

All patients had at least 1 invasive infection of the lung, liver, lymph nodes, blood, gastrointestinal tract, or bone requiring prolonged intravenous antimicrobial therapy (Table I). Moreover, by using the parameter of intractable infections or steroid-dependent CGD,[16] 70% of our patients had high-risk disease at the time of transplantation. Three of 11 patients had required mechanical ventilation for respiratory failure. The mean age at transplantation was 3.8 years, with a range of 11 months to 13 years.

Transplantation

Four of 11 patients received MRD stem cell transplantation from 6/6 HLA-identical siblings. Seven patients received a 10/10 HLA-genoidentical graft from an unrelated donor without clinical evidence of CGD. All related donors had normal oxidative burst activity and no evidence of the carrier state. IFN-γ was discontinued in all patients 7 to 10 days before HSCT.

All patients received a busulfan-based myeloablative conditioning regimen combined with cyclophosphamide and cytarabine for MRD transplant recipients or fludarabine for MUD transplant recipients. Busulfan was administered on days −9 to −6 before transplantation at a starting dose of 0.8 to 1 mg/kg, and cyclophosphamide was administered at a dose of 45 mg/kg at days −3 and −2 for MRD transplant recipients and at a total dose of 50 mg/kg at days −5 to −2 for MUD transplant recipients. Dosing of busulfan was based on actual weight unless actual weight exceeded ideal weight by 30%. For these patients, we calculated the adjusted weight (ideal body weight plus 25%). Busulfan was administered intravenously every 6 hours for 16 doses. Blood samples were obtained with the first and ninth doses to modify the dose of busulfan to an area under the curve of 900 to 1200 μmol/min/L. All patients received anticonvulsant therapy while receiving busulfan. Cytarabine was administered at 2 g/m^2 for 4 doses on days −6 to −4 for MRD recipients. Fludarabine was administered at 30 mg/m^2 at days −5 to −2 for MUD recipients. All patients received alemtuzumab (anti-CD52) at 3 mg (if <15 kg), 5 mg (if >15 kg but <30 kg), or 10 mg (if >30 kg) at days −5 to −2 to improve engraftment and decrease the risk of GvHD. Additional GvHD prophylaxis consisted of cyclosporine A and prednisone in patients receiving an MRD graft and cyclosporine A and methotrexate in patients receiving an MUD graft. Bone marrow grafts had a median total nucleated cell dose of 6×10^8/kg, with a range of 5.0×10^7/kg to 1.5×10^{10}/kg.

Chimerism was established either by means of fluorescent *in situ* hybridization for sex chromosome or by using short tandem repeats for allele DNA sequencing. The presence of oxidase-positive neutrophils was detected by means of flow cytometry with the use of the dihydrorhodamine oxidation assay and reported as geometric mean fluorescence or the SI.

After HSCT, recovery of B and T cells was measured by using flow cytometric analyses, as described by Fleisher and Oliveira.[17] Lymphoproliferative responses were measured with isolated mononuclear cells. These cells were cultured in microwell plates loaded with diluted mitogen or specific antigens. The PHA and Concanavalin A (ConA) responses were measured by using tritiated thymidine incorporation. A PHA or ConA response was considered normal if there was 75,000 cpm or greater tritiated thymidine incorporation. After transplantation, we evaluated specific antigen responses to tetanus and *Candida* species in all patients. Specific antigen results were considered normal if the SI was 2 or greater.

Statistical analysis

The time to neutrophil or platelet engraftment was defined as the time from transplantation to the time when the neutrophil count reached 500 cells/μL for 3 consecutive days and the time when the unsupported platelet count reached 20,000 cell/mm^3, respectively. The cumulative probability for the time to neutrophil or platelet engraftment were estimated and plotted by using the Kaplan-Meier method. The median times to engraftment were compared between MRD and MUD transplant recipients by using the Wilcoxon method. The immune reconstitution data (CD3 T-cell, CD4, T-cell, or PHA responses) were repeated measurements and analyzed by using nonlinear mixed-effects models with autoregressive correlation of log 1. The patterns of immune reconstitution data over time suggest a nonlinear logistic growth model.[18] The estimated curves fit the data reasonably well. The times for the curves to hit a fixed boundary were estimated by using the Δ method, and the difference between MRD and MUD transplant recipients was compared by using the Wald asymptotic test.

TABLE I. Characteristics of 11 children with CGD

	Age at CGD diagnosis	Age at HSCT	Sex	Ethnicity	Genetics	SI at diagnosis
1	2 wk	30 mo	M	W	X-linked gp91^{phox}	2
2	14 mo	45 mo	M	W	X-linked gp91^{phox}	2
3	8 mo	41 mo	F	H	AR gp67^{phox}	1
4	36 mo	8.3 y	M	H	X-linked gp91^{phox}	1
5	6 mo	11 mo	M	H	X-linked gp91^{phox}	1
6	6 wk	6.4 y	F	A	AR (no molecular testing)*	3
7	4.5 y	5.9 y	M	W	X-linked gp91^{phox}	1
8	2.5 mo	18 mo	M	H	X-linked (no molecular testing)*	2
9	9 mo	7.4 y	M	W	X-linked (no molecular testing)*	1
10	3 wk	50 mo	M	W	X-linked gp91^{phox}	1
11	2.5 mo	13 y	M	W	X-linked (negative molecular testing, negative sequencing)*	1

A, African American; *AIHA*, autoimmune hemolytic anemia; *F*, female; *H*, Hispanic; *I&D*, Incision and drainage; *M*, male; *Meds RX*, treated with medications; *URTI*, upper respiratory tract infection; *W*, white.

*Patient 6 had no molecular testing and no family history of CGD. Patients 8, 9, and 11 all had mothers with Neutrophil burst test findings consistent with X-linked carrier status and 2 populations of granulocytes (normal and poor oxidative burst). Patient 9 had a younger brother who died at 1 year of age with *Burkholderia cepacia* and granulomas in the liver/lungs. Patient 11 had negative *CYBB*/*CYBA* mutations, and full sequencing did not identify a known CGD-associated mutation.

†Comorbidities before HSCT.

‡Comorbidities after HSCT.

§High-risk patients (ongoing treatment/prophylaxis for known infections and/or significant pulmonary inflammation by imaging: ongoing granulomas).

RESULTS

Engraftment

A neutrophil count of greater than 500 cells/μL (Fig 1) was reached at a median of 18 days for the cohort, with a median of 17 days (range, 13-24 days) and 18 days (range, 16-21 days) for MRD and MUD transplant recipients, respectively (MRD vs MUD, $P = .65$). A platelet count of greater than 20,000 cells/mm^3 (Fig 2) was reached at a median of 16 days for the cohort, with a median of 16 days (range, 14-22 days) and 21 days (range, 12-40 days) for MRD and MUD transplant recipients, respectively (MRD vs MUD, $P = .52$). All patients achieved greater than 95% donor chimerism before day 100. Beyond day +100, donor chimerism for 2 MRD transplant recipients decreased but stabilized at a mean of 70% at 22 and 59 months after HSCT. Donor-derived chimerism has remained stable in all patients, with no further stem cell infusions required to improve engraftment and a median follow-up time of 4 years (range, 1-8 years).

Neutrophil oxidative burst activity after HSCT was assayed by using dihydrorhodamine and was normal by day 100 for all patients. Fig 3 shows pre- and post-HSCT mean dihydrorhodamine SIs for our cohort. All patients, including those with mixed chimerism status after transplantation, had sustained normal dihydrorhodamine activity.

Grade I acute GvHD of the skin developed in 4 of 11 patients. Three of these patients received an unrelated product, but all of them responded to topical steroids. No patient had grade II or greater acute GvHD or chronic GvHD.

Clinical outcomes and adverse events

The conditioning regimen was well tolerated apart from 1 patient who experienced seizures during busulfan administration. The median busulfan area under the curve after the first dose for the group was 934 μmol/min/L. Four patients needed dose adjustments (2 in the sibling donor group and 2 in the unrelated donor group), in 3 of whom the dose was increased by 30%. A requirement for dose adjustment had no discernible effects on engraftment kinetics, GvHD, or complications after transplantation.

TABLE I. *(Continued)*

Pre-HSCT infections (isolation; age at diagnosis)	Comorbidities	HSCT type/risk	Outcome after HSCT
Staphylococcus aureus–induced otitis (culture; 2 y)	Molluscum,† URTI-associated wheezing†	MRD	Mixed chimerism
Burkholderia cepacia–induced pneumonia (lung biopsy; 11 mo)	Asthma,†,‡ pulmonary nodules†,‡	MUD	Skin grade 1 acute GvHD
Serratia marcescens–related osteomyelitis (bone aspirate; 8 mo)	Iron deficiency anemia,† transaminitis,† chronic lung cysts†,‡	MRD§	Adenovirus in plasma (resolved w/o intervention)
Aspergillus species–induced pneumonia (lung biopsy; 5 y)	G tube for poor feeding,† chronic pulmonary nodules,†,‡asthma†,‡	MUD§	Cytomegalovirus reactivation (prescription medications) *Aspergillus* species–induced pneumonia
Staphylococcus aureus–induced abscess (surgical wound I&D; 6 mo)	Perirectal abscesses,† chronic diarrhea†	MUD	Skin grade 1 acute GvHD
Burkholderia cepacia–induced pneumonia (lung biopsy; 5 y) *Aspergillus niger*–induced pneumonia (lung biopsy; 5.5 y)	Neonatal HIV exposure,† chronic cystic lung disease†,‡	MUD§	EBV reactivation (resolved w/o intervention)
Burkholderia cepacia–induced osteomyelitis, bacteremia (bone I&D; 4.5 y)	Weakness,† voriconazole sensitivity,† chronic lung disease†,‡	MUD§	AIHA therapy with oral steroids (14 mo after HSCT)
Candida albicans–induced abscess and bacteremia (surgical I&D; 1 y)	Lymphadenitis,† perirectal abscess,† transaminitis†	MRD§	Cytomegalovirus reactivation (meds RX) Mixed chimerism
Burkholderia gladioli–induced osteomyelitis (bone biopsy; 5.8 y)	Hearing loss,†,‡ eosinophilic cystitis,† drug–induced lupus†	MUD	Skin grade 1 acute GvHD
Serratia marcescens–induced liver abscess (liver biopsy; 2 wk) *Aspergillus fumigatus*–induced pneumonia (lung biopsy; 1 mo)	CGD colitis,† transaminitis,† asthma†,‡	MRD§	Skin grade 1 acute GvHD Busulfan–related seizures Adenovirus of stool (resolved w/o intervention)
Presumed *Aspergillus* species-induced pneumonia (lung biopsy with hyphae; 8 y); *Staphylococcus aureus*–induced perirectal abscess (surgical I&D; 10 y)	Perirectal abscess,† recurrent lymph adenitis,† chronic pulmonary nodules†,‡	MUD§	Hashimoto thyroiditis (17 mo after HSCT)

One patient had a relapse of *Aspergillus* species–induced pneumonia before engraftment (patient 4 in Table I) with bilateral pulmonary infiltrates, high fevers, and impaired respiratory function. Treatment with amphotericin, echinocandin, and imidazole was combined with granulocyte infusions and additional donor CD34-selected cells, leading to complete and sustained pulmonary recovery. No other patient had serious infection or other grade 4 toxicities.

Immune reconstitution

The estimated time for $CD3^+$ T-cell numbers reaching 300/μL was 114 days (95% CI, 44.6-183.4 days) for MRD transplant recipients and 185.9 days (95% CI, 123.4-248.4 days) for MUD transplant recipients ($P = .12$, not significant). The estimated time for $CD3^+$ T-cell numbers reaching 500/μL was 147.5 days (95% CI, 89.0-206.0 days) for MRD transplant recipients and 225.3 days (95% CI, 168.9-281.8 days) for MUD transplant recipients ($P = .13$, not significant). The estimated time for $CD4^+$ T-cell numbers reaching 300/μL was 81.2 days (95% CI, −17.1 to 179.4 days) for MRD transplant recipients and 215.1 days (95% CI, 123.4-248.4 days) for MUD transplant recipients ($P = .09$, not significant). The estimated time for $CD4^+$ T-cell numbers reaching 500/μL is 139.5 days (95% CI, 50.9-228.1 days) for MRD transplant recipients and 291.3 days (95%, 194.8-387.9 days) for MUD transplant recipients ($P = .12$, not significant). The data and estimated curves are shown in Fig 4, *A* and *B*. The function of these T cells was measured by using the *in vitro* proliferation responses to mitogens (PHA) and specific antigens (tetanus). Responses to log counts per minute of PHA at a concentration of 10 μg/mL are shown in Fig 4, *C*. The estimated time to normalization was 148.2 days (95% CI, 85.8-210.5) for MRD transplant recipients and 169.7 days (95% CI, 108.9-230.5 days) for MUD transplant recipients ($P = .96$, not significant). CIs to indicate the variability of the T-cell recovery and function are wide likely because of the small sample size. Hence we cannot correlate cell numbers with the strength of immune responses. Specific antigen responses after exposure to tetanus and *Candida* species and mitogen responses to ConA in addition to other immune parameters are shown in Table II[19] and show normalization for the majority of patients at last follow-up.

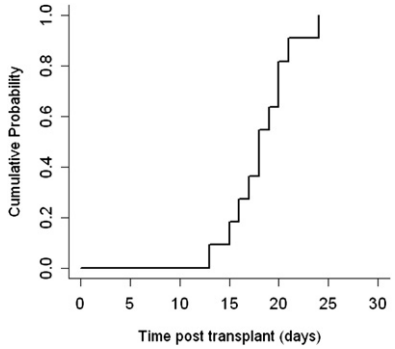

FIG 1. Neutrophil engraftment. Cumulative incidence of neutrophil engraftment (defined as neutrophil count >500/μL) occurred at a median time of 18 days (range, 13-24 days).

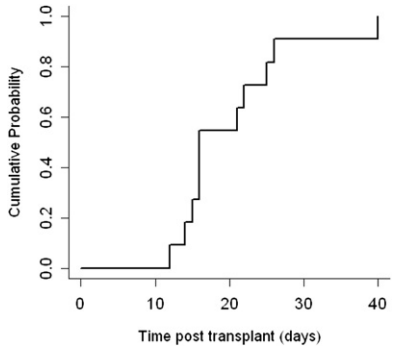

FIG 2. Platelet engraftment. Cumulative incidence of platelet engraftment (defined as platelet count >20,000/mm^3) occurred at a median time of 16 days (range, 12-40 days).

Survival, activity level, and educational status

All patients are well at a mean follow-up of 4 years (range, 1-8 years). Quality of life has improved for all patients, reaching normal activity without special care (Lansky score of 100%). All but 1 patient currently attends school (9 in elementary school and 1 in high school). One patient is receiving home schooling because of the family's social needs.

DISCUSSION

The long-term survival of patients with CGD remains poor despite improvements in conventional therapies. Although gene therapy holds promise as a curative option, success has been limited, with patients with CGD losing gene-corrected cells within 6 months of treatment or having myelodysplastic syndrome and acute myelogenous leukemia.[20,21] Hence HSCT currently remains the only curative treatment. To date, HSCT has largely been recommended only to patients with CGD with an HLA-MRD who also had more than 1 life-threatening infection in the past or intractable infections, severe granulomatous disease with organ dysfunction or steroid dependence, nonavailability of specialist care, or noncompliance with antibiotic prophylaxis.[16] We now report 100% survival for 11 patients undergoing HSCT, for whom 7 received grafts from MUDs. Stable engraftment with full donor chimerism was observed in 9 of 11 patients with a median follow-up time of 2.5 years (range, 1-9 years). There was no acute GvHD beyond grade I or chronic GvHD or graft failure, and in all but 1 patient with recurrent aspergillosis, the HSCT was uneventful.

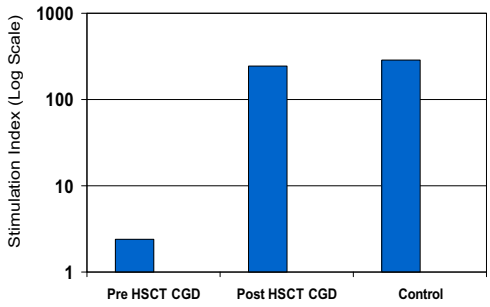

FIG 3. Neutrophil oxidative burst by dihydrorhodamine. Pre-HSCT mean SIs averaged less than 2 before HSCT and corrected to and were sustained at normal levels after HSCT for all patients.

Seger et al[22] previously reported 85% overall survival in 27 patients with CGD receiving an HSCT mainly consisting of genotypically identical related grafts (n = 25), and Soncini et al[15] reported survival in 9 of 10 European patients with CGD after MUD HSCT with myeloablative conditioning and standard acute GvHD prophylaxis mainly consisting of cyclosporine and methotrexate with an incidence of grade II acute GvHD of approximated 30%.

Our MUD conditioning regimen of busulfan, cyclophosphamide, fludarabine, and alemtuzumab is a regimen that has been associated with high engraftment rates and a low risk of significant GvHD when no matched sibling is available and to is well tolerated when used as conditioning for patients with primary immunodeficiencies.[23] Incorporation of cytarabine as part of triple-chemotherapy conditioning for primary immunodeficiencies in MRD transplant recipients has been used by our group for more than a decade. When combined with lower doses of cyclophosphamide and alemtuzumab (a humanized mAb that eliminates cells expressing CD52, including T and B lymphocytes, eosinophils, monocytes, natural killer cells, and some dendritic cells), these agents have been well tolerated and produced a high level of engraftment and low GvHD in patients undergoing transplantation for nonmalignant diseases. Because alemtuzumab administered before transplantation remains at lytic levels in peripheral blood for more than 21 days after administration, it produces depletion of both recipient and donor immune system cells, favoring engraftment and a low rate of GvHD, respectively.[24,25] Such immune depletion can be associated with a high level of posttransplantation infection.[25-27] In this series we monitored viral reactivation routinely and observed the expected rate. Reactivation was controlled with medical treatment, where feasible (Table I), and no viral disease occurred.

In this patient population our main goal is engraftment, and therefore alemtuzumab was not adjusted according to graft type to reduce the incidence of graft failure. To date, we have not had any graft failure or rejection in our CGD population. We adjust the alemtuzumab dosage according to graft type when transplantation is used to treat patients with leukemia because graft failure is less common in these heavily pretreated patients.

We observed a faster immune recovery for CD4$^+$ T cells compared with that seen in earlier reports of recovery after alemtuzumab conditioning,[24,25] perhaps because of the lower dose used in our trial and the younger age of our patient population. Although

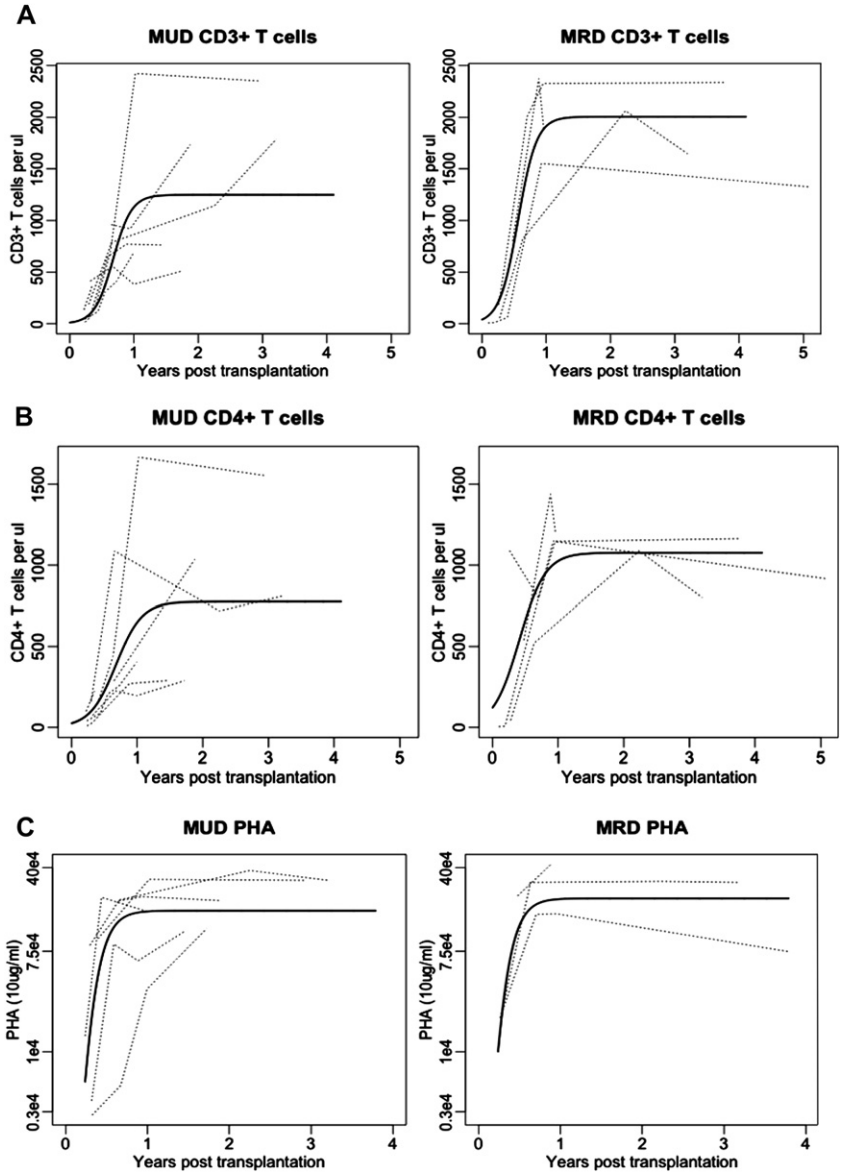

FIG 4. Immunoreconstitution. $CD3^+$ T-cell **(A)** and $CD4^+$ T-cell **(B)** absolute number recovery and function measured by proliferative responses to mitogen (PHA, 10 μg/mL; **C**) after HSCT are shown.

there was a trend for a more prompt $CD3^+$ and $CD4^+$ T-cell recovery after transplantation in the MRD transplantation group compared with the MUD transplantation group, this trend did not reach statistical significance. There was similar T-cell function in both transplantation groups measured based on responses to PHA. Consistent with these observations, we observed no discernible increase in the incidence of infections in the MUD versus MRD transplant recipients. Immunoglobulin supplementation was suspended by 12 months after HSCT, and specific antibody response to vaccine challenge was documented for most patients. Although virus-specific cytotoxic T lymphocytes derived from the stem cell donor or a third party[28,29] might be of benefit for posttransplantation infections in intensely lymphodepleted patients, these cells were not required or used in this patient cohort.

There is no reason to believe that the excellent outcome we observed was attributable to inadvertent selection bias in the patients in terms of clinical severity or mutational status. The majority of patients were X-linked $gp91^{phox}$ with baseline dihydrorhodamine values of less than 2 and a high incidence of severe intractable infections and granulomas.

Our series reports the use of HLA-MUDs as an alternative stem cell source, but umbilical cord blood or haploidentical donor sources might also be suited for subjects lacking a fully HLA-matched donor, and addition of an alemtuzumab conditioning regimen might be beneficial in this setting as well.[24] There has been a debate among clinical immunologists about whether to treat patients with CGD with antimicrobial agents and preserve their lives or whether to pursue a more definitive mode of therapy with HCST. Previous concerns over the failure of HSCT for CGD other than from HLA-identical siblings have placed definitive therapy on hold, which encourages physicians to continue to treat the numerous and serious infection with

TABLE II. Immune parameters at last follow-up

Patient no.	Age at HSCT	Age at follow-up	ANC	CD3	CD4 (abs#)	CD19 (abs#)	PHA† 10 μg/mL	ConA† 50 μg/mL	Candida species (SI)	Tetanus (SI)
1	30 mo	5 y	2,262	1.647 (1.4-3.7)	709 (0.7-2.2)	538 (0.4-1.4)	297,328	267,247	4,516	30,944
2	45 mo	8 y	1,367	1.789 (1.2-2.6)	810 (0.65-1.5)	0.635 (0.2-.86)	304,466	313,285	2,586	43,710
3	41 mo	6 y	2,690	1.874 (1.4-3.7)	1.192 (0.7-2.2)	2.121 (0.4-1.4)	426,433	324,072	NA	763
4	8.3 y	10 y	2,650	1.034 (1.2-2.6)	0.423 (0.65-1.5)	0.103 (0.4-1.4)	152,145	NA	NA	NA
5	11 mo	3 y	4,080	2.531 (1.4-3.7)	1.554 (0.7-2.2)	0.446 (0.4-1.4)	309,721	113,562	5,931	749
6	6.4 y	9 y	10,301	1.801 (1.4-3.7)	0.959 (0.65-1.5)	0.773 (0.4-1.4)	166,508	141,519	11,093	61,579
7	5.9 y	6 y	1,820	0.367* (1.4-3.7)	0.222* (0.7-2.2)	0.403* (0.4-1.4)	306,364	242,380	770	118
8	18 mo	5 y	2,690	2.336 (1.4-3.7)	1.164 (0.7-2.2)	1.267 (0.4-1.4)	74,320	80,528	281	304
9	7.4 y	10 y	3,040	0.507 (1.2-2.6)	0.288 (0.65-1.5)	0.879 (0.4-1.4)	118,145	50,525	247	14,350
10	50 mo	9 y	2,770	1.326 (1.2-2.6)	0.916 (0.65-1.5)	0.781 (0.4-1.4)	253,455	83,238	2,342	24,138
11	13 y	15 y	2,429	1.054 (1-2.2)	0.645 (0.5-1.3)	0.679 (0.1-0.6)	277,627	178,714	NA	NA

Values in parentheses are normal values presented as 10th and 90th percentiles. Subset counts (number of cell per microliter $\times$ 10¯3).[19]
abs#, Absolute number of cells; *NA*, not available.
*Studies performed while taking steroids for autoimmune hemolytic anemia.
†Proliferation responses are expressed as log of counts per minute.

appropriate antibiotics, antifungal agents, and antiviral drugs. However, these prolonged treatments are frequently insufficient to prevent infection of lymph nodes, lungs, and the liver, and these often demand surgical removal of diseased tissue. In addition to the physical problems of such patients, adolescents and young adults with CGD might decline strict adherence to drug therapies and often express giving up on life because of their inability to lead normal lives free of frequent infections, clinic visits, and hospital admissions. The excellent outcome with low complication rates observed in our patient cohort supports the argument for early HSCT in young patients with CGD. Although our report is of a single-center retrospective study with a small number of patients and will clearly require confirmation in multicenter prospective studies, it is now our practice to consider HSCT (both MRD and MUD) after the first life-threatening infection and before the onset of end-organ damage, allowing permanent cures of CGD to become more commonplace.

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Clinical implications: MUDs have been proved to be as good as MRDs in HSCT, broadening the choice of definitive therapy for all patients with CGD.

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