

# Allogeneic Haematopoietic Stem Cell Transplantation as Therapy for Chronic Granulomatous Disease—Single Centre Experience

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**Abstract** Chronic granulomatous disease (CGD) is phagocytic cell metabolic disorder resulting in recurrent infections and granuloma formation. This paper reports the favourable outcome of allogeneic transplantation in six high-risk CGD patients. The following donors were used: HLA-matched, related (two) and unrelated (three), and HLA-mismatched, unrelated (one). One patient was transplanted twice using the same sibling donor because of graft rejection at 6 months after reduced-intensity conditioning transplant (fludarabine and melphalan). Myeloablative conditioning regimen consisted of busulphan and cyclophosphamide. Stem cell source was unmanipulated bone marrow containing:  $5.2 (2.6–6.5) \times 10^8$  nucleated cells,  $3.8 (2.0–8.0) \times 10^6$  CD34+ cells and  $45 (27–64) \times 10^6$  CD3+ cells per kilogramme. Graft-versus-host disease prophylaxis consisted of cyclosporine A and, for unrelated donors, short course of methotrexate and anti-T-lymphocyte globulin. Mean neutrophil and platelet engraftments were observed at day 22 (20–23) and day 20 (16–29), respectively. Pre-

existing infections and inflammatory granulomas resolved. With the follow-up of 4–35 months (mean, 20 months), all patients are alive and well with full donor chimerism and normalized superoxide production.

**Keywords** Immunological deficiency · chronic granulomatous disease · haematopoietic stem cell transplantation · children

## Introduction

Chronic granulomatous disease (CGD) is X-linked or autosomal recessive inherited immune deficiency caused by mutations in the genes encoding the various subunits of the NADPH oxidase system of phagocytic cells responsible for the killing of phagocytosed microorganisms. CGD occurs with an estimated frequency of one in 250,000 live births. This defect is associated with significant morbidity and mortality so the predicted life expectancy is of about 25–30 years of age. The disease is characterized by recurrent, severe and life-threatening, bacterial and fungal infections with granuloma formation in different organs [1].

Usual sites of infections, mainly caused by catalase-positive microorganisms (e.g. *Aspergillus* sp., *Staphylococcus* sp., *Salmonella* sp.), are lungs, skin, gastrointestinal tract, liver and lymph nodes. Persistent inflammatory reaction to infection may lead to colitis with subsequent growth failure, gastric outlet obstruction, lung disease and granuloma formation [2, 3].

Conventional management for patients with CGD consists of lifelong anti-infectious prophylaxis with cotrimoxazole or

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antibiotics with intracellular activity, antimycotics steroids and/or interferon- $\gamma$  (IFN- $\gamma$ ). Nevertheless, the annual mortality is still 2–5%, and only 50% of patients are alive at 30 years [4, 5]. Therefore, there is a need for more effective therapies. Allogeneic haematopoietic stem cell transplantation (HSCT) is the only curative treatment for CGD with the excellent outcome noted in patients asymptomatic at transplantation. In a high-risk group of CGD patients (adults with organ dysfunction and/or patients with active inflammation and infections), the transplant-related mortality (TRM) about 30% is noted [6, 7].

Here, we report on six young CGD patients successfully treated with allogeneic HSCT with full correction of the phagocytic function before onset of organ dysfunction due to chronic inflammation.

### Patients and Methods

Patient 1, a 2-year-old boy, was diagnosed at the age of 1.5 years to have X-linked CGD. He presented with recurrent lymphadenopathy, pneumonia, diarrhoea and skin infection. On admission, the generalized lymphadenopathy, mild hepatomegaly and multiple granulomas of the lungs were observed.

Patient 2, a 13-year-old girl, was diagnosed as having CGD at the age of 2 years. In the past, she had *Salmonella* Typhimurium gastroenteritis, recurrent lymphadenopathy, cervical abscess, sinusitis with *Aspergillus fumigatus*, frequent pneumonias, sepsis, herpes and varicella infections and multiple skin infections. She was admitted to our department before transplantation with sinusitis due to aspergillosis despite intensive antifungal treatment (amphotericin B and voriconazole).

Patient 3, a 5-year-old boy, was diagnosed with CGD at the age of 10 months after surgical removal of multiple abscesses of lymph nodes. His mother's older brother and her first son died of severe infections in early childhood. He has been repeatedly hospitalized with skin abscesses, meningitis, gastroenteritis (*Salmonella* Typhimurium) and severe pneumonias.

Patient 4, a 3.5-year-old boy with X-linked CGD (Xp21.1, subtype X91+), was diagnosed 6 months ago. The family history indicated that his mother's brother died at the age of 3 years because of infection. The patient experienced recurrent lung and skin infections. The CT abdominal scan performed at the age of 3 years due to fever and abdominal pain showed hepatomegaly with multiple nodular areas.

Patient 5, a 1.5-year-old boy, was diagnosed with X-linked CGD at the age of 6 months. He had in the past sinusitis, kidney, liver abscess and multiple skin infections.

Patient 6, a 2-year-old boy with CGD, was diagnosed 6 months ago after serious gastroenterocolitis (*Salmonella* Typhimurium). This boy is a cousin of patient 3.

### Diagnosis

In all patients, the diagnosis of CGD was established on the basis of clinical symptoms and the lack of chemiluminescence response to latex stimulation of blood measurement as described previously [8] and confirmed by nitroblue tetrazolium (NBT) reduction test [9].

### Prophylaxis and Treatment

The antibacterial and antimycotic treatment or prophylaxis was introduced immediately after diagnosis of CGD and continued until transplantation.

### Transplantation

The stem cell transplantation and collection of data before treatment were performed after written informed consent of parents and patient 2. The information on the beneficial effects of conventional antibacterial/antifungal prophylaxis/treatment, the risk of allografting, especially in the presence of overt infections or inflammatory symptoms, and a lack of sibling donors was also provided. Donor and recipient HLA matching was performed by molecular typing of HLA classes I (A, B, Cw) and II loci (DRB1, DQB1). Patients 1 and 6 underwent bone marrow transplantation from a sibling donor with HLA-identical genotype. Patients 2, 4 and 5 received HLA-identical bone marrow from unrelated donors, and patient 3 was transplanted with bone marrow from mismatched unrelated donor [patient's HLA: A\*0201\*2402, B\*3906\*4402, Cw\*0702\*0704, DRB1\*1601, DQ\*0502; donor's HLA: A\*0201\*2402, B\*3901\*4402, Cw\*1203\*0704, DRB1\*1601, DQ\*0502]. The characteristics of patients and donors are shown in Table I. Patients were nursed in a high-efficiency, particle-air-filtered protected environment. During transplantation period, leucocyte-depleted and irradiated blood products were used. Colistin at 100,000 U/kg/day was given as an oral gut decontamination. Prophylaxis regimen also included cotrimoxazole, acyclovir, fluconazole, heparin and, when needed, intravenous immunoglobulin (IVIG) substitution until immune reconstitution. Patient 2 with fungal sinusitis at transplantation was treated with voriconazole and caspofungin until engraftment. Five of six patients received busulphan-based myeloablative conditioning regimen, combined with cyclophosphamide. Patient 1 was conditioned according to reduced-intensity (RI) protocol with the use of fludarabine and melphalan. Details of conditioning regimens are shown in Table II. Stem cell

**Table I** The characteristics of patients and donors

	Type of donor	Age (years)		Gender		CMV status		EBV status		Blood groups AB0 (Rh)	
		R	D	R	D	R	D	R	D	R	D
Patient 1	MSD	2/3 <sup>a</sup>	6/7 <sup>a</sup>	M	F	+	+	+	+	A (-)	A (-)
Patient 2	MUD	13	26	F	F	-	+	+	+	0 (-)	0 (+)
Patient 3	MMUD	5	28	M	F	+	-	+	+	0 (+)	0 (+)
Patient 4	MUD	4	21	M	M	-	+	-	+	A (+)	A (-)
Patient 5	MUD	1	26	M	F	-	+	+	+	B (+)	0 (+)
Patient 6	MSD	2	12	M	F	+	+	+	-	0 (+)	B (+)

R recipient, D donor, CMV cytomegalovirus, EBV Epstein–Barr virus, MSD matched sibling donor, MUD matched unrelated donor, MMUD mismatched unrelated donor, + positive, - negative

<sup>a</sup> At second transplantation

source was unmanipulated bone marrow containing  $4.6 (2.6\text{--}6.5)\times 10^8$  nucleated cells (NS),  $3.3 (2.0\text{--}4.9)\times 10^6$  CD34+ cells and  $44 (26\text{--}64)\times 10^6$  CD3+ cells per kilogramme of recipient body weight (b.w.). The cell doses for patient transplanted with an RI were as follows:  $3.0\times 10^8$  NS,  $4.0\times 10^6$  CD34+ and  $26\times 10^6$  CD3+ cells per kilogramme of body weight. Graft-versus-host disease (GvHD)

prophylaxis consisted of cyclosporine A (CsA) beginning on day -1 (patients 1, 5 and 6) and on day -4 (patients 2, 3 and 4). The plasma level of CsA was maintained between 150 and 200  $\mu\text{g/mL}$ , and this therapy was continued until 3 months (patients 1 and 6) and 6 months (patients 2, 3, 4 and 5). The CsA was tapered rapidly because of gradually decreasing chimerism in patient 1 and slowly in patients 2,

**Table II** Conditioning regimens

	Regimen	Total dose	Daily dose	Administration	Days
Patient 1	Flu	150 mg/m <sup>2</sup>	30 mg/m <sup>2</sup>	i.v. in 30 min	-7, -6, -5, -4, -3
	Mel	140 mg/m <sup>2</sup>	70 mg/m <sup>2</sup>	i.v. in 1 h	-3, -2
Patient 1 <sup>a</sup>	Bu	20 mg/kg	5 mg/kg	p.o. q 6 h	-9, -8, -7, -6
	Cy	200 mg/kg	50 mg/kg	i.v. in 1 h	-5, -4, -3, -2
	ATG <sup>b</sup>	7.5 mg/kg	3.75 mg/kg	i.v. in 8–10 h	-3, -2
Patient 2	Bu	16 mg/kg	4 mg/kg	p.o. q 6 h	-9, -8, -7, -6
	Cy	200 mg/kg	50 mg/kg	i.v. in 1 h	-5, -4, -3, -2
	ATG <sup>b</sup>	10 mg/kg	2.5 mg/kg	i.v. in 8–10 h	-4, -3, -2, -1
Patient 3	Bu	20 mg/kg	5 mg/kg	p.o. q 6 h	-7, -6, -5, -4
	Cy	120 mg/kg	60 mg/kg	i.v. in 1 h	-3, -2
	ATG <sup>c</sup>	60 mg/kg	20 mg/kg	i.v. in 8–10 h	-3, -2, -1
Patient 4	Bu	20 mg/kg	5 mg/kg	p.o. q 6 h	-9, -8, -7, -6
	Cy	200 mg/kg	50 mg/kg	i.v. in 1 h	-5, -4, -3, -2
	ATG <sup>c</sup>	60 mg/kg	20 mg/kg	i.v. in 8–10 h	-3, -2, -1
Patient 5	Bu	20 mg/kg	5 mg/kg	p.o. q 6 h	-9, -8, -7, -6
	Cy	200 mg/kg	50 mg/kg	i.v. in 1 h	-5, -4, -3, -2
	ATG <sup>b</sup>	10 mg/kg	2.5 mg/kg	i.v. in 8–10 h	-3, -2, -1
Patient 6	Bu	20 mg/kg	5 mg/kg	p.o. q 6 h	-9, -8, -7, -6
	Cy	200 mg/kg	50 mg/kg	i.v. in 1 h	-5, -4, -3, -2

Flu fludarabine, Mel melphalan, Bu busulphan, Cy cyclophosphamide, ATG rabbit anti-T-cell globulin

<sup>a</sup> At second transplantation

<sup>b</sup> Genzyme

<sup>c</sup> Fresenius

3, 4, 5 and 6. Additionally, patients transplanted from unrelated donors received short course of methotrexate at 10 mg/m<sup>2</sup>.

The chimerism was studied at +30, 100, 180 and 360 days after standard HSCT and every 1 month after non-myeloablative transplantation by karyotyping (fluorescence in situ hybridization) or analysis of informative microsatellite DNA sequences with the use of standard techniques. Neutrophil function and NK-, T- and B-cell reconstitution measurements were performed at the same time schedule and then every year. Lymphocyte subsets were measured by flow cytometry including CD3+, CD4+, CD8+, CD19+ and CD16+56+ cells. The presence of oxidase-positive neutrophils was detected by NBT tests. Immunoglobulin levels (IgG, IgA, IgM) were measured by nephelometry.

**Results**

**Engraftment**

Engraftment with full chimerism and functioning neutrophils were observed in all patients. Haemopoietic recovery occurred within a median time of 22 days (range, 20–23 days) to neutrophil count >500/μL and within a median time of 20 days (range, 16–29 days) to platelet count >20,000/mL (Table III). The donor-derived haemopoiesis and the normal NBT reduction remained in five patients. In patient 1, after initial engraftment, chimerism fell to 14% despite cessation of CsA and donor lymphocyte infusion (DLI) in four increasing doses every 4–6 weeks: first, 0.2×10<sup>6</sup>/kg; second, 1.0×10<sup>6</sup>/kg; third, 1.8×10<sup>6</sup>/kg and fourth, 5.0×10<sup>6</sup>/kg. In this patient, after the first HSCT, the lymphadenopathy and granulomas resolved despite of slow rejection. The second transplant from the same sibling donor after myeloablative conditioning was performed 8 months after the first HSCT

(Table II). Unmanipulated bone marrow containing, per kilogramme of recipient b.w., 6.0×10<sup>8</sup> NS, 8.0×10<sup>6</sup> CD34+ cells and 53×10<sup>6</sup> CD3+ cells was infused. Neutrophil engraftment occurred on day +23 and platelets on day +29 (Table III). Full donor chimerism and normal value of NBT test were observed on day +30.

**Survival**

There was no episode of serious conditioning-related toxicity. For patients 1, 2, 4, 5 and 6, transfusion requirement was low, with median of 2 (range, 1–3) red blood cell concentrates and median of 4 (range, 3–7) of platelet transfusions. Patient 3 received eight red blood cell and six platelet concentrates because of haemorrhagic diarrhoea due to acute GvHD (aGvHD). He had also rotavirus infection and cytomegalovirus reactivation treated with gancyclovir with good response. No febrile episodes or exacerbations of preexisting infections were observed. The median length of hospitalization was 36 days (range, 33–61 days). In patient 2, the short episode of haemorrhagic cystitis grade II was observed at 3 months after transplantation but resolved after symptomatic therapy. All patients are alive and well with a median follow-up of 20 months (range, 4–35 months) after HSCT. In all patients, the lymphadenopathy and granulomas resolved and therapy of refractory pre-existing infections is not required.

**Graft-Versus-Host Disease**

Two patients had symptoms of aGvHD. Patient 2 presented with mild aGvHD (increasing level of bilirubin and AAT) with good response to steroids. Patient 3 developed severe grade IV acute GvHD with the gut, liver and skin involvement that required therapy with prednisolone, mycophenolate mofetil, tacrolimus and oral budesonide, and which finally resolved after anti-TNF-α therapy

**Table III** Engraftment and chimerism

	Engraftment (day after HSCT)		NBT +30 day (N, >0.1)	Donor's chimerism			
	Neutrophil >500/μL	PLT >20/μL		+30 days (%)	+100 days (%)	+180 days (%)	+1 year (%)
Patient 1	22	–	0.154	100	37	14	–
Patient 1 <sup>a</sup>	23	29	0.226	100	100	100	100
Patient 2	20	17	0.318	100	100	100	100
Patient 3	21	21	0.207	100	100	100	100
Patient 4	22	18	0.218	100	100	100	100
Patient 5	22	16	0.315	100	100	–	–
Patient 6	21	29	0.143	100	100	–	–

HSCT haematopoietic stem cell transplantation, PLT platelets, NBT nitroblue tetrazolium test, N normal value

<sup>a</sup> At second transplantation

(etanercept) and infusion of mesenchymal cells ( $0.3 \times 10^6$ /kg). Again, the limited chronic GVHD of skin developed but gradually responded to treatment without continuing sequelae.

### Immunological Reconstitution

Since engraftment, all patients demonstrated normal NBT test. The IVIG replacement therapy was discontinued shortly after transplantation. Patients transplanted from unrelated donors showed subnormal count of lymphocyte T, B and NK cells during first year after HSCT. The normalization of lymphocyte number was faster in patient transplanted from matched related donor. All patients were included in revaccination protocol according to our schedule [10, 11]. In patients 1 and 2, the basic programme of vaccination against tetanus, diphtheria and hepatitis B virus was completed. Antibody production against these pathogens was adequate.

### Discussion

CGD has been extensively studied during the last years. Because gene therapy is still in its infancy, allogeneic HSCT remains the only curative therapy for CGD. The benefits of HSCT like normal growth and improvement in quality of life with no need for medication are clear. This is in contrast to non-transplanted patients who remain on lifelong antimicrobial prophylaxis, with a continued risk of infections resistant to the prophylactic treatment that require frequent hospitalization [5, 12].

Although the first reports of transplantation in CGD were not so optimistic, the use of matched sibling donor improved the survival (above 90%) especially in children without severe infections and at an early stage of disease. As the chance of finding a matched related donor is less than 25%, and haploidentical HSCT is considered as a high risk due to delayed immune reconstitution and graft failure, the unrelated donor transplantation has been established as an alternative procedure [13]. However, the use of unrelated donor could be associated with a higher risk of complications after HSCT [14].

In our study, four patients underwent transplantation from unrelated donors (three matched and one mismatched). This mismatched unrelated donor was used in situation of a serious clinical status of the recipient and after four years of unsuccessfully searching for a matched unrelated donor. Finally, the decision of mismatched donor HSCT was regarded as a life-saving procedure.

The EBMT advocated myeloablative regimens, mostly consisting of busulphan and cyclophosphamide allografts from HLA-matched related donors, which provided excel-

lent results in low-risk CGD patients [15, 16]. In opinion of other researchers, the myeloablative conditioning was associated with the high rates of severe acute GVHD and pulmonary infections leading to the TRM of above 30% especially in advanced CGD patients with active inflammation or infections [6, 17].

The therapeutic option of allogeneic transplantation after reduced-intensity conditioning (RIC) may be the alternative for CGD patients with coexisting severe infections and organ damage [18, 19]. However, the RIC regimens performed until now have shown a significant risk of incomplete engraftment with the donor haematopoietic cells or graft rejection and GvHD, particularly if DLI has to be used to ensure engraftment. Nevertheless, the RIC HSCT is usually enough to improve clinical status and resolve the inflammation and infections before the graft rejection [20–22]. Moreover, additional standard myeloablative HSCT could be performed as a salvage therapy if second transplant is required [23].

In the present group, patient 1 was transplanted twice from the HLA-identical sibling. The first time was with RIC and subsequently with myeloablative conditioning. After transplantation with RIC, the graft rejection occurred and donor's chimerism decreased from 100% to 14% within 6 months despite withdrawal of immunosuppression and DLI. The subsequent transplantation led to a rapid engraftment. Five remaining patients who received myeloablative HSCT donors engrafted around 22 days after transplantation, and the stable full donor chimerism and normal phagocyte function were observed at 30 days.

In our opinion, for patients with CGD, the optimal time of transplantation is critical. In most cases of CGD, HSCT is postponed until the patient is chronically ill. However, if transplantation is delayed, the chances of severe infections, the risk of GVHD and other serious transplant complications significantly increase [6].

The severe GVHD remains a special risk in CGD patients, possibly because CGD phagocytes have a specific propensity for increased production of TNF- $\alpha$ . Moreover, its level significantly rose in patients with granulomatous colitis or aspergillosis. Therefore, TNF-antagonist therapy may be beneficial if given as early treatment for GVHD and other complications [24, 25].

All presented patients are now judged as cured by clinical status and phagocytic function. No conditioning toxicity was observed despite the use of myeloablative regimens.

We believe that it is desirable to perform HSCT in young patients with proven diagnosis of CGD before the onset of life-threatening infections and organ damage due to chronic inflammation. As the HSCT procedure is safe enough, it may challenge the common view that HSCT is indicated in

CGD patients only after severe clinical episode confirming the diagnosis.

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