Clinical and immunological outcome after paediatric stem cell transplantation in inborn errors of immunity

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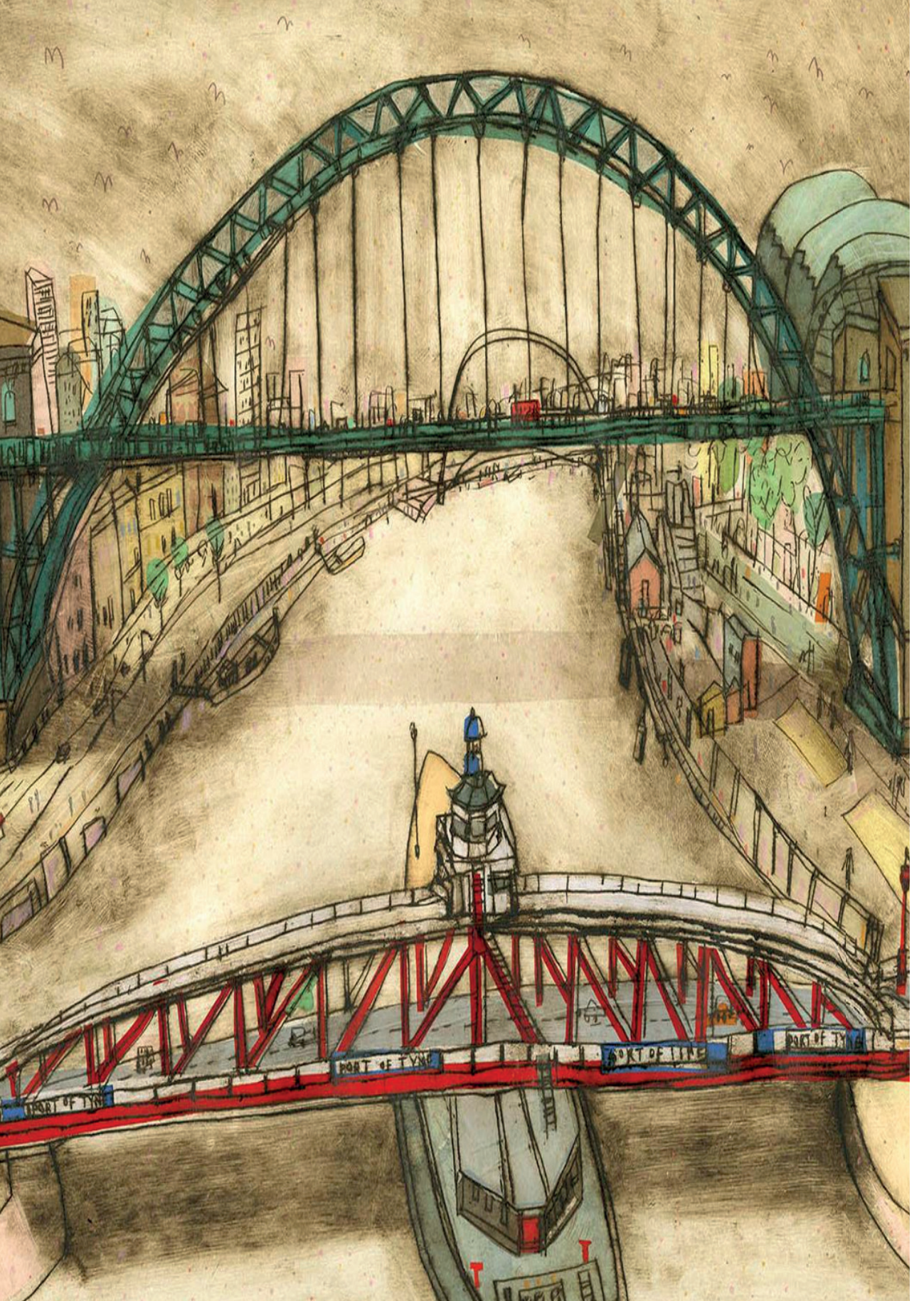
Part 2

Practice pattern evolution and long-term disease outcomes in haematopoietic cell transplantation for inborn errors of immunity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Chapter 2

Two decades of excellent transplant survival in children with chronic granulomatous disease: A report from a supraregional immunology transplant center in Europe

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Blood 2019; 133 (23): 2546-2549

Abstract

Haematopoietic cell transplantation (HCT) is the only established curative therapy for patients with chronic granulomatous disease (CGD). We studied the transplant survival, long-term graft function, immune reconstitution and autoimmune disease post-transplant at our center. Fifty-five children with CGD were included. Median age at transplant was 5.3 years (range, 0.6-18.0). 45 (82%) had X-linked and 10 (18%) had autosomal recessive CGD. The 5-year OS for the cohort was 89% (95% CI, 67-95%). Age at transplant less than 5 years old was associated 100% survival compared to older children (p=0.04). The 5-year event-free survival for the cohort was 77% (95% CI 62-87%). All 7 patients with slipping chimerism received successful second procedures (3 had unconditioned stem cell boost infusion and 4 had fully conditioned second transplant). The median age of long-term survivors was 14 years (range, 2-36 years) and there were no late deaths. The median donor myeloid chimerism after first successful HCT (n=43) was 92%% (range 30-100%). The 1- and 5-year cumulative incidences of autoimmune diseases were 9% and 12% respectively. Our cohort confirmed that HCT performed in an experienced immunology transplant center is safe and provides long-term cure for children with CGD.

Introduction

Chronic granulomatous disease (CGD), an inherited immunodeficiency resulting from defects in the NADPH oxidase complex rendering phagocytes deficient in producing the superoxide anion necessary for normal killing of bacterial and fungal microorganisms, leads to severe and recurrent infections, inflammatory granulomatous complications and autoimmune diseases.(1) It is associated with substantial morbidity and premature death. Haematopoietic cell transplantation (HCT) is the only long-term curative therapy, but utility was historically limited by high rates of graft failure and transplant-related morbidity and mortality. Transplant survival and graft outcome have improved dramatically over the past 10 years, due to reduced toxicity conditioning regimens, detailed graft selection hierarchy, superior HLA matching technology, better cell-dosed grafts, greater availability of grafts, improved supportive care and more effective anti-microbial therapy. We studied transplant survival post-HCT for CGD in a supra-regional immunology transplant center in the United Kingdom.

Study design

We report outcomes of patients with CGD who received their first HCT between 1998-2017 at the Great North Children's Hospital, Newcastle upon Tyne, one of two supra-regional transplant centers in the UK for children with primary immunodeficiency. Outcomes of interest were overall survival (OS), event-free survival (EFS), haematopoietic recovery, toxicities, graft-versus-host disease (GvHD), long-term survival, graft function, post-transplant immune reconstitution and autoimmune disease post-transplant. OS was defined as survival from first HCT to last follow-up or death. An event was defined as death or second procedure for slipping chimerism. Cox proportional-hazard modelling was used to analyse predictors of OS and ES. Variables included for predictor analysis were: year of transplant (1998-2007 versus 2008-2017), age at transplant, donor (family versus unrelated donor), conditioning (myeloablative conditioning (MAC) versus reduced toxicity conditioning (RTC)), stem cell source (marrow versus peripheral blood), total nucleated cell dose (TNC) and CD34 cell dose. Multiple linear regression modelling was used to analyse the impact of conditioning, stem cell source and cell doses on long-term graft function after first successful HCT. CD3, CD4, CD8, CD19, CD27/CD45RA and CD16/56 enumeration were measured routinely. All data analyses were performed using STATA version 14.2.

Results and discussions

Fifty-five children with CGD were included, none were excluded. A detailed description of transplant characteristics is summarized (Table 1). Median age at transplant was 5.3 years (range, 0.6-18.0). 45 (82%) had X-linked and 10 (18%) autosomal recessive CGD. Twelve (22%) had growth failure (defined as weight less than fifth centile for age and gender) at the time of transplant. Of 34 who underwent colonoscopy, 31 (91%) had biopsy proven colitis. Four (7%) had biopsy proven granulomatous lung inflammation. One had undefined acute necrotising encephalitis. Prior to 2007 various conditioning regimens were used, with 21 (38%) patients receiving pharmacokinetically guided intravenous (IV) busulfan (Bu) and IV cyclophosphamide with or without serotherapy. From 2007 the conditioning regimen was switched to Fludarabine-Treosulfan-Alemtuzumab with post-HCT GvHD prophylaxis using ciclosporin (CSA) and mycophenolate mofetil (MMF) for family and unrelated donors (n=24, 44%). Fludarabine-Treosulfan-Thiotepa-ATG-Rituximab was used for CD3 TCRαβ CD19 depleted haploidentical grafts (n=4, 7%). Of these 4 patients, one received CSA/MMF and the remaining 3 did not receive any post-HSCT GvHD prophylaxis. The median day to neutrophil and platelet engraftment was 16 days (range, 9-37), and 18 days (range, 10-139) respectively. Ten (20%) patients had grade II-IV acute GvHD, 5 (9%) had grade III-IV acute GvHD. None had chronic GvHD. Only one patient who received Busulfan-based conditioning had veno-occlusive disease. Eleven (20%) had CMV viraemia, 5 (9%) adenoviraemia and 5 (9%) EBV viraemia.

The 5-year OS was 89% (95% CI, 67-95%) (Figure 1a), rising to 100% for children transplanted at <5 years of age (n=28) versus 81% (95%CI, 60-92%) for the children ≥5 years of age (n=27) (p=0.04) (Figure 1b). The OS was comparable between matched family (88%, 95% CI, 61-97%) and unrelated donor transplants (89%, 71-95%) (Figure 1c). The 4 haploidentical transplants were successful. Year of transplant (p=0.13), conditioning (p=0.58), stem cell source (p=0.57), TNC (p=0.69) and CD34 cell dose (p=0.52) were not associated with OS. All five deaths were due to transplant-related complications. The median age at transplant of deceased patients was 10.0 years (range 8.4-18 years). The 5-year EFS for the cohort was 77% (95% CI 62-87%). No variables were associated with EFS. All 7 patients with slipping chimerism received successful second procedures (3 had unconditioned stem cell boost infusion and 4 had fully conditioned second transplant).

Median age of long-term survivors was 14 years (range, 2-36 years) with median duration of follow-up of 6.5 years (range, 0.32-19.5 years). There were no late deaths. None had clinical evidence of colitis. Of the 11 survivors who were older than 21 years of age, 6 (55%) had unassisted successful pregnancy themselves or with their partners (4 received Busulfan-

Cyclophosphamide, 1 Busulfan-Fludarabine and 1 had Fludarabine-Melphalan). Median donor myeloid chimerism after first successful HCT (n=43) was 92%% (range 30-100%). MAC was the only variable associated with higher donor myeloid chimerism (p=0.036). MAC (p=0.002) and TNC (p=0.03) were associated with higher donor T-lymphocyte chimerism (supplemental figure 1 and supplemental table 1). For patients who received unconditioned stem cell boost (n=3), the median myeloid chimerism was 52% (ranges, 30-100%) and the median T-lymphocyte chimerism was 26% (range 16% to 100%). For patients who received conditioned second transplant (=4), the median myeloid chimerism was higher at 89% (ranges, 30-100%) and the median T-lymphocyte chimerism was 65% (range 26-100%). Longitudinal immune-reconstitution results were available for 42 patients of survivors after first successful HCT (supplemental figure 2).

The 1- and 5-year cumulative incidence of autoimmune diseases was 9% and 12% respectively, significantly less than that reported in a recent study (figure 1d). (2) Three (5%) had immune cytopenia in first year post-HCT. whilst 3 (5%) had autoimmune endocrinopathy (2 thyroid dysfunction; 1 type 1 diabetes mellitus). Two patients with immune haemolysis achieved remission with intravenous immunoglobulin and steroid while 1 with immune haemolysis and thrombocytopenia needed additional Rituximab. None had evidence of immune cytopenia at last follow-up. Autoimmune endocrinopathy occurred one year post-HCT (median 3.9 years; range, 1.4-7.1). One patient with hypothyroidism received thyroxine replacement, 1 with Grave's disease was treated with radioiodine and 1 with type 1 diabetes mellitus received insulin.

The ability of donor-derived neutrophils to replace recipient's defective neutrophils makes HCT a superior therapy compared to conventional standard of care using antimicrobial therapy. Previous studies demonstrated that non-transplanted children have more serious infections, episodes of surgery, poorer growth and reduced quality of life compared to transplanted children.(3-5) Estimated survival of non-transplanted patients was 88% at 10 years and 55% at the age of 30 years.(6) In this study, our findings emphasize that HCT performed in an experienced immunology transplant center is safe and provides long-term cure for children with CGD. Alternative donors using unrelated and parental haploidentical donors are associated with excellent survival comparable to family donors. X-linked carrier family donors should be avoided as they have inflammatory and autoimmune symptoms and excessive fatigue. (7-9) As young age at HCT is associated with favourable outcome, HCT should be performed as early as possible before the onset of disease-related organ damage. In our center, all newly diagnosed CGD and newborn CGD are recommended for HCT with either matched donor or haploidentical donor if no suitable matched donor available. Family screening plays an important role in advancing the transplant care for children with CGD.

Table 1: Patient and transplantation characteristics and outcome after first HCT in children with CGD (N=55)

Patient characteristics	
Year of transplant	
1998-2007, n (%)	17 (31)
2008-2017, n (%)	38 (69)
Male, n (%)	51 (93)
Inheritance	
X-linked CGD, n (%)	45 (82)
Autosomal recessive CGD, n (%)	10 (18)
Age at transplant, months, median (range)	5.3 (0.6-18.0)
Donor characteristics	
Type of donor	
Matched family donor, n (%)	20 (36)
Unrelated donor, n (%)	31 (56)
Haploidentical donor, n (%)	4 (8)
Stem cell source	
Marrow, n (%)	29 (53)
PB, n (%)	24 (43)
CB, n (%)	2 (4)
Stem cell dose	
Marrow	
TNC, x 10^8/kg, median (range)	5.0 (1.6-24.4)
CD34, x 10^6/kg, median (range)	4.3 (0.75-53.0)
PB	
TNC, x 10^8/kg, median (range)	10.3 (1.2-22.8)
CD34, x 10^6/kg, median (range)	8.0 (3.0-29.2)
Transplant characteristics	
Conditioning regimen	
Myeloablative conditioning (MAC)	
Busulfan-Cyclophosphamide, n (%)	21 (38)
Fludarabine-Treosulfan-Thiotepa, n (%)	4 (7)
Reduced toxicity conditioning (RTC)	
Treosulfan-fludarabine, n (%)	24 (45)
Busulfan-fludarabine, n (%)	4 (7)
Treosulfan-cyclophosphamide, n (%)	1 (2)
Fludarabine-melphalan, n (%)	1 (2)
Serotherapy	
None, n (%)	9 (16)
ATG, n (%)	4 (8)
Alemtuzumab, n (%)	42 (76)
GVHD prophylaxis	
None, n (%)	3 (5)
CSA alone, n (%)	2 (4)
CSA + MTX, n (%)	16 (29)
CSA + MMF, n (%)	33 (60)
CSA + steroid (for CB), n (%)	1 (2)

Patient characteristics	
Haematopoietic recovery	
Days to neutrophil recovery, median (range)	16 (9-37)
Days to platelet recovery, media (range)	18 (10 - 139)
Transplant-related complications	
Acute GvHD	
Grade II-IV, n (%)	10 (20)
Grade III-IV, n (%)	5 (9)
Chronic GvHD[2]	0
Veno-occlusive disease, n (%)	1 (2)
Number of patients received second procedures for slipping chimerism, n (%)	7 (13)
Number of patients received unconditioned stem cell boost infusion	3
Myeloid chimerism prior to unconditioned stem cell boost infusion, %, median (range)	17 (15-23)
Number of patients received fully conditioned second transplant	4
Myeloid chimerism prior to fully conditioned second transplant, %, median (range)	11 (0-13)
Cause of death (n=5)	
Multi-organ failure	2
Acute GvHD	1
Pulmonary haemorrhage	1
Post-transplant lymphoproliferative disease	1

ATG: anti-thymocyte globulin (Grafalon) for haploidentical transplant; CB: cord blood; CGD: chronic granulomatous disease; CSA: ciclosporin; MMF: mycophenolate mofetil; MTX: methotrexate; PB: peripheral blood; TNC: total nucleated cell dose

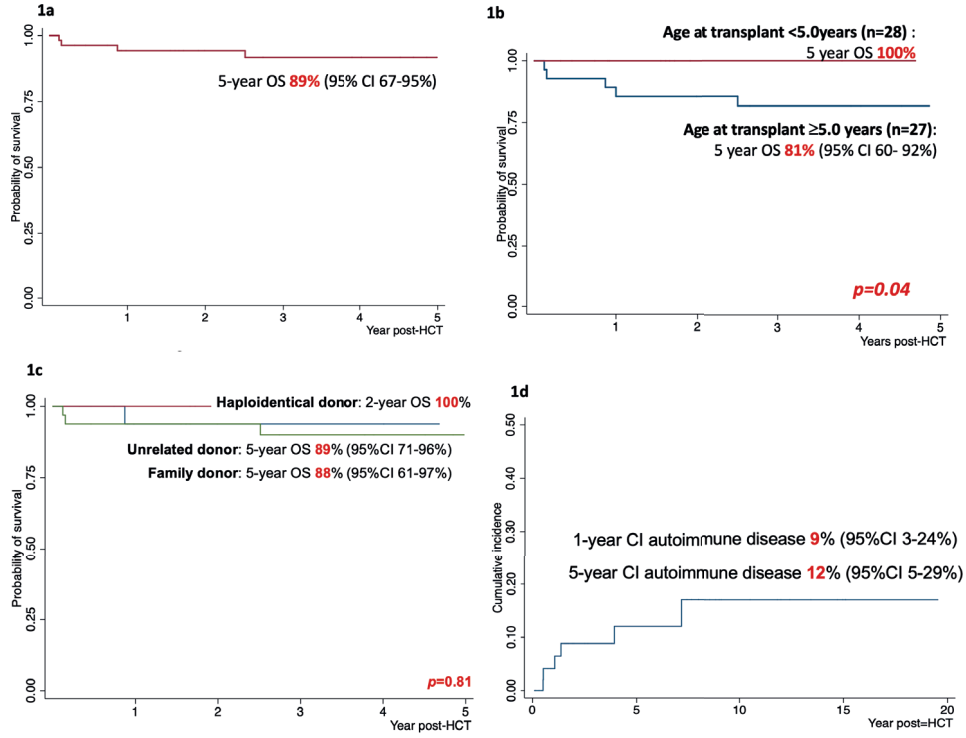
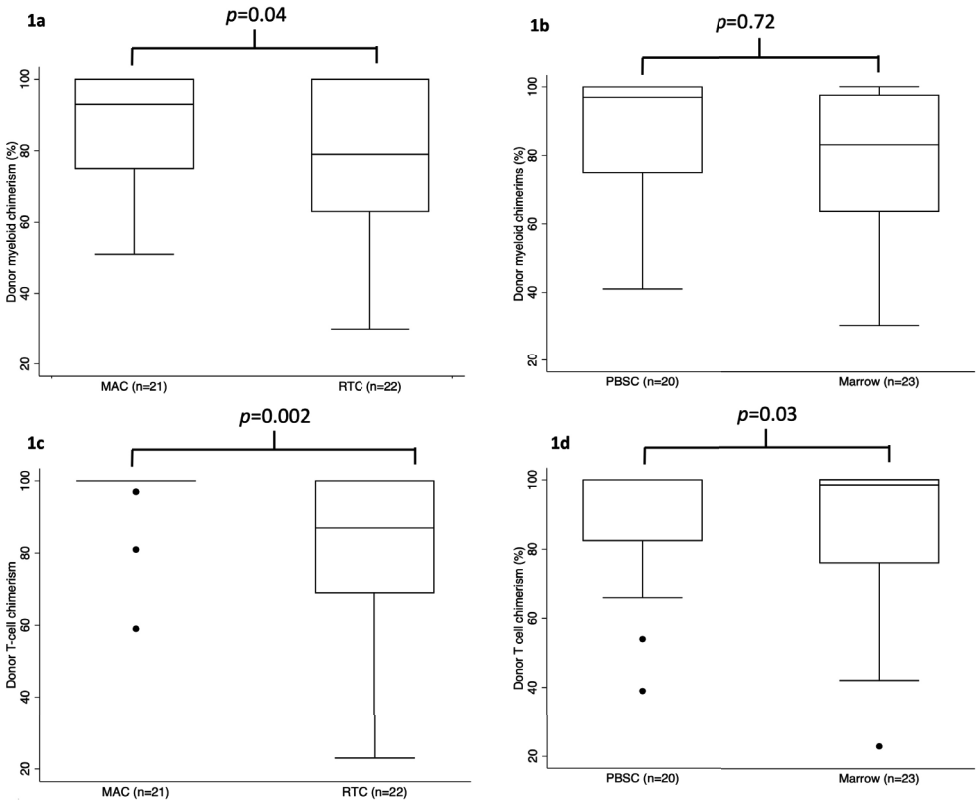


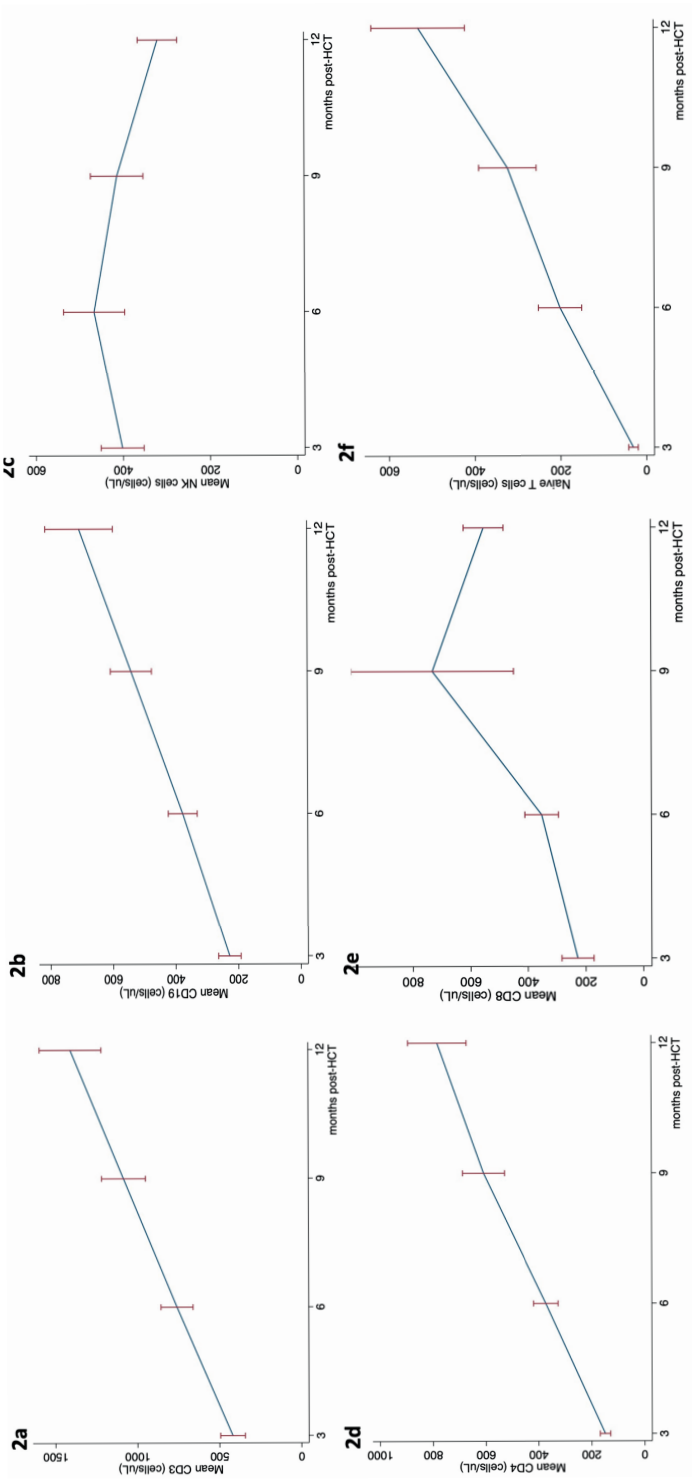
Figure 1: OS of entire cohort (1a), OS according to age at transplant (1b) and donor type (Ic) and cumulative incidence of autoimmune disease (1d)

Supplemental table 1: Impact of conditioning, stem cell source and cell doses on donor chimerism after first successful HCT for patients with CGD (n=43)

	Coefficient	95% confidence interval	*p*-value
Donor myeloid chimerism			
MAC vs RTC	-13.6	-25.4 to -0.92	0.04
PBSC vs marrow	-2.3	-15.5 to 10.8	0.72
TNC	1.12	-0.12 to 2.37	0.08
CD34	-0.01	-0.99 to 0.95	0.97
Donor T cell chimerism			
MAC vs RTC	-21.5	-34.4 to -8.74	0.002
PBSC vs marrow	-0.48	-20.1 to 8.40	0.41
TNC	1.37	0.13 to 2.61	0.03
CD34	-0.67	-1.64 to 0.20	0.17



Supplemental figure 1: Impact of conditioning and stem cell source on the donor myeloid chimerism (1a and 1b) and donor T cell chimerism (1c and 1d)



Supplemental figure 2: Mean and standard error (SE) of CD3+ cells (2a), CD19 cells (2b), NK cells (2c), CD4 cells (2d), CD8 cells (2e) and naïve T cells (2f) measured at different time points post-transplant

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