Journal of Clinical Immunology (2019) 39:448–458
https://doi.org/10.1007/s10875-019-00635-2

ORIGINAL ARTICLE

Role of Allogeneic Hematopoietic Stem Cell Transplant for Chronic Granulomatous Disease (CGD): a Report of the United States Immunodeficiency Network

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Received: 29 May 2018 / Accepted: 21 April 2019 / Published online: 20 May 2019

Abstract

Purpose Chronic granulomatous disease (CGD) is a primary immunodeficiency for which allogeneic hematopoietic stem cell transplant (HSCT) offers potential cure. Direct comparison of HSCT to non-HSCT management in the North American population was performed to identify clinical factors associated with overall survival (OS) and transplant-related survival (TRS).

Methods Retrospective review of CGD subjects enrolled in the United States Immunodeficiency Network. Survival was estimated by the Kaplan-Meier method and modeled by proportional hazards regression.

Results We identified 507 patients (66% *CYBB* mutants) diagnosed in 1953–2016. Fifty underwent allogeneic HSCT. Median follow-up was 9.1 years after diagnosis (0–45.8 years). OS was negatively associated with *CYBB* mutation (HR = 6.25; $p = 0.034$) and not associated with HSCT (88% v. 85% ± HCT) (HR = 1.26; $p = 0.65$). Transplant at ≤ 14 years old was associated with improved TRS (93% v. 82% at $T + 60$ months) (HR = − 4.51; $p = 0.035$). Patients transplanted before 15 years old had fewer severe infections pre-HSCT (mean 0.95 v. 2.13; $p = 0.047$). No mortality was reported in patients receiving stem cells from matched siblings. Infection incidence declined post-HSCT in subjects with greater than or equal to four infections pre-HSCT ($p = 0.0010$). Compared to non-HSCT patients ≥ 15 years old, post-transplant survivors had higher mean performance score (93.2 v. 85.9; $p = 0.0039$) and lower frequency of disability (11% v. 52%; $p = 0.014$).

Conclusion Allogeneic HSCT was associated with reduced infection incidence and improved functional performance, but not with a change in overall survival. Transplant-related survival was elevated in patients undergoing HSCT before 15 years old. Consider HSCT prior to late adolescence in patients with severely diminished reactive oxygen intermediate synthesis, particularly if a matched sibling is available.

Keywords Chronic granulomatous disease · primary immunodeficiency · hematopoietic stem cell transplant · overall survival · graft-versus-host disease · USIDNET

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10875-019-00635-2) contains supplementary material, which is available to authorized users.

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Introduction

Chronic granulomatous disease (CGD) is a primary immunodeficiency characterized by phagocyte dysfunction. Defects in nicotinamide adenine dinucleotide phosphate (NADPH) oxidase impair generation of superoxide radicals in phagolysosomes, compromising formation of the microbicidal oxidative burst. Five structural proteins comprise the following enzymes: membrane-bound $gp91^{phox}$ and $p22^{phox}$ (forming cytochrome b_{558}) and cytosolic $p40^{phox}$, $p47^{phox}$, and $p67^{phox}$ [1].

X-linked mutations in *CYBB* (encoding the catalytic domain $gp91^{phox}$) account for over two thirds of North American cases and are often associated with severe manifestations early in life [2, 3]. Autosomal recessive mutations in *NCF1* (encoding $p47^{phox}$) comprise approximately 20% of defects and are typically associated with a less severe phenotype [3, 4]. Residual reactive oxygen intermediate (ROI) production largely mediates the effect of genotype on phenotype and has been directly associated with survival as a continuous variable [5].

Patients have increased susceptibility to infections by catalase-producing organisms (such as *Staphylococcus*, *Burkholderia*, *Serratia*, *Nocardia*, and *Aspergillus*) with predilection for the lungs, liver, and soft tissue [6]. Dysregulation of pro-inflammatory cascades [1] and defective apoptosis [7, 8] predispose patients to non-infectious granulomata, typically in the lungs and gastrointestinal and genitourinary tracts [9, 10].

The annual incidence of CGD in the USA is estimated to be 1 in 200,000 live births [9]. Infection (namely, due to *Aspergillus*) has historically been the leading cause of death [3, 9, 10]. *CYBB* mutation [2], hepatic abscess, and portal hypertension [11, 12] have been associated with increased mortality. Improved diagnosis, prophylaxis with interferon gamma [13, 14] itraconazole [15], and advanced antimicrobials have helped to extend survival to over 50%, 30 years after diagnosis [9, 10, 16–22]. However, treatment of hyperinflammatory disease remains a challenge, as immunosuppression (particularly tumor necrosis factor-alpha blockade) enhances infection and mortality risk [23]. Nearly 50% of patients encounter symptomatic inflammatory bowel disease [24]. Poor growth [21, 25, 26] and poor quality of life [21, 27] are also common.

The accumulation of physical and psychosocial injury in early adulthood presents a pivotal management decision to clinicians. Traditional indications for allogeneic hematopoietic stem cell transplant (HSCT) include greater than or equal to one life-threatening infection, steroid-dependent or refractory granulomatous disease, organ dysfunction due to hyperinflammation, and prophylaxis non-adherence [10]. European registry analyses comparing HSCT to non-HSCT management have demonstrated benefits in infection frequency, growth [25], and survival [28] following transplant. However, this data has not been replicated in the North American population, and factors impacting transplant-related survival (TRS) remain to be explored.

We present evaluation of the largest North American CGD cohort reported at the time of authorship, enrolled in the United States Immunodeficiency Network (USIDNET) registry, a program of the Immune Deficiency Foundation. Primary objective was to evaluate overall survival (OS) in patients treated with or without allogeneic HSCT. Secondary objectives were to identify clinical factors associated with overall and transplant-related survival, to evaluate infection incidence before and after transplant, and to analyze quality of life in patients treated with or without HSCT.

Methods

A retrospective review of the USIDNET registry was performed. All CGD patients enrolled in the database from its inception in 1992 through data extraction in October 2016 were included. Individual enrolling institutions obtained an IRB approval and informed consent for registry inclusion from all participants. The IRB approval from the USIDNET and University Hospitals Cleveland Medical Center was obtained.

OS was measured from the date of diagnosis to the date of death and censored at the date of last follow-up for survivors. TRS was measured from the date of allogeneic HSCT to the date of death and censored at the date of last follow-up for survivors. Date of diagnosis and date of transplant were used because our primary objective was to compare survival based on discrepant treatment modality (HSCT v. non-HSCT). Survivor distribution was estimated by the Kaplan-Meier method [29].

Cox proportional hazards regression was used to identify factors associated with mortality among all evaluable patients, assessing allogeneic HSCT, *CYBB* mutation, liver abscess, *Aspergillus* infection, granulomatous gastrointestinal disease, chronic pulmonary disease, and birth year (before v. during or after 2003). We selected this stratification because in 2003, the efficacy of itraconazole prophylaxis for prevention of invasive fungal infections in CGD patients was established [15].

Improved TRS has been observed in patients transplanted prior to adulthood [30–35]. Consequently, TRS was compared by the Kaplan-Meier method in patients undergoing HSCT at ≤ 14 years old versus at > 14 years old. The association of TRS with donor, graft, conditioning regimen, birth year (before v. during or after 2003), *CYBB* mutation, and the presence of severe infection or any granulomatous disease pre-HSCT was evaluated by univariate and bivariate Cox proportional hazards regression, using age at HCT in years and the number of infections pre-HCT as continuous variables for bivariate models. Severe infection was defined as fungal pneumonia, fungemia, visceral abscess, sepsis, or meningitis. We did not have sufficient documentation to identify pharmacologically refractory infections. Clinical characteristics of the HCT cohort stratified by age at first stem cell infusion (termed "T_0") were evaluated, using Pearson's chi-squared test for categorical variables, Mann-Whitney *U* test for

non-normally distributed continuous variables, and two-sided Student's *t* test for normally distributed continuous variables.

For comparison of infection rates pre-HSCT and post-HSCT in subjects with greater than or equal to four infections before HCT, Poisson regression with generalized estimating equations for inference was used to handle potential correlations of outcomes observed pre- and post-transplant in the same patient. The infection rate was further estimated with adjustment for the effects of age at diagnosis, sex, and race.

To analyze functional performance over time, post-HSCT and non-HSCT subjects alive at the last documented visit were divided according to age at the last follow-up: 0–10 years, 11–20 years, 21–30 years, 31–40 years, and > 40 years. The mean performance score (Lanksy or Karnofsky) at last visit was calculated for each age division. Within the post-HCT and non-HCT groups, one-way ANOVA compared the age-stratified means. Tukey's method was used for post hoc analysis of significantly different means. The mean performance score and proportion of patients with disability at last visit were compared between post-HCT and non-HCT subjects ≥ 15 years old using Student's *t* test and chi-square analysis, respectively. All tests were two-sided, with *p* values ≤ 0.05 considered statistically significant [36] and interpreted with 95% confidence intervals (CIs). Statistical analysis was performed using SAS software (version 9.2; SAS Institute, Cary, NC).

Results

Demographics

From 19 enrolling institutions (Table 5 in the Appendix), 507 CGD patients diagnosed in 1953–2016 were identified. One third ($n = 169$) had birth year ≥ 1990. Diagnosis was made by nitroblue tetrazolium reduction and/or dihydrorhodamine flow cytometry at the median age of 2 years (0.1–34.2 years). The median follow-up after diagnosis was 9.1 years (0–45.8 years). Most mutations were in *CYBB* (66%), followed by *NCF1* (15%). Compared to non-HSCT subjects, the HSCT group had a higher proportion of males (94% v. 83%; $p = 0.044$) and patients with granulomatous gastrointestinal disease (52% v. 19%; $p < 0.001$). The frequency of identified mutations and recorded interferon gamma treatment did not differ between HSCT and non-HSCT subjects. The median year of diagnosis was higher in HSCT (2001, range 1970–2012) than in non-HCT (1988, range 1953–2016) patients ($p < 0.001$) (Table 1).

Fifty patients diagnosed in 1970–2012 underwent allogeneic HSCT from 1982 to 2016. Disseminated fungal infection or fungal pneumonia was the most commonly reported indication for transplant ($n = 16$, 32%), followed by gastrointestinal granulomata ($n = 13$, 26%). The median age at transplant was 13.1 years (0.6–37.3 years). Thirty-six transplants (72%) were performed between 2012 and 2016. The median follow-up after T_0 was 18.5 months (0–402.5 months) (Table 2). Myeloablative conditioning (MAC) was used for umbilical cord blood (UCB) transplants. Reduced-intensity conditioning (RIC) was commonly employed for non-UCB transplants.

Overall Survival

Evaluable data for survival analysis was available for 302 patients, 38 of whom underwent HSCT. OS started to progressively decline in the second decade after diagnosis and was estimated to be 65% 30 years after diagnosis (Fig. 1a). There was no significant difference in likelihood OS based on treatment with or without allogeneic HSCT when all genotypes (Fig. 1b), *CYBB* mutants alone (Fig. S1), and patients born between 2003 and 2016 (Fig. S2) were analyzed by the Kaplan-Meier method.

Sixty-nine non-HSCT patients (15.1%) died (Table 1). The cause of death was recorded for 43 subjects and was infectious in 41 cases (95%), including pneumonia ($n = 17$), sepsis ($n = 12$), and disseminated fungal infection ($n = 11$). *Aspergillus* species ($n = 15$) and *Burkholderia cepacia* ($n = 6$) were the most frequently reported organisms causing mortality. One case of hepatocellular carcinoma and one case of hepatic failure were documented.

After adjusting for the effects of confounders in the general cohort, *CYBB* mutation was associated with an increased hazard of dying (HR = 6.25 [95% CI = 1.14, 33.33]; $p = 0.034$). HSCT, *Aspergillus* infection, and liver abscess were not independently associated with mortality hazard (Table 3).

Transplant-Related Survival

The majority of transplant-related mortality (TRM) occurred in the first 18 months post-HSCT, with no deaths recorded after $T + 24$ months (Fig. 1c). Evaluable data for TRS was available for 34 patients, as the date of transplant was not clearly documented for four patients. TRS at $T + 60$ months was elevated in patients who underwent HSCT at ≤ 14 years old, compared to those > 14 years old at T_0 (HR = 4.51; $p = 0.035$) (Fig. 1d). Diagnostic delay and frequency of *CYBB* mutation did not differ between the HSCT groups stratified by age at T_0. The frequency of peripheral blood stem cell (PBSC) use was higher in patients > 14 years old at T_0 (73% v. 36%; $p = 0.010$) (Table 2).

Donor, graft, conditioning regimen, and the presence of any severe infection or granulomatous disease pre-HSCT were not associated with TRM in univariate (Table S1) or bivariate (Table 3) regression analyses. Using age at T_0 and the number of severe infections pre-HSCT as continuous variables, increasing age at T_0 was associated with a modestly increased hazard of dying (HR = 1.10 [95% CI = 1.01, 1.20]; $p = 0.036$) (Table 3).

Six male patients who underwent HSCT died at the median of 9.6 months (0.5–19.1 months) after transplant. Four were *CYBB* mutants, and one had *CYBA* mutation. Chronic graft-versus-host disease (GvHD) was implicated in the deaths of two patients

Table 1 Baseline demographics, compared by allogeneic HSCT status

	Total ($n = 507$)	HSCT ($n = 50$)	Non-HSCT ($n = 457$)	p value†	95% CI
Male, *n* (%)	426 (84)	47 (94)	378 (83)	0.044*	− 0.061, 17.06
White (non-Hispanic), *n* (%)	350 (69)	34 (68)	315 (69)	0.88	
X-linked inheritance, *n* (%)	337 (66)	36 (72)	301 (66)	0.39	
CYBB mutation (gp91^{phox}), *n* (%)	337 (66)	36 (72)	301 (66)	0.39	
NCF1 mutation (p47^{phox}), *n* (%)	61 (15)	3 (6)	58 (13)	0.15	
NCF2 mutation (p67^{phox}), *n* (%)	12 (3)	1 (2)	11 (2)	1.00	
CYBA mutation (p22^{phox}), *n* (%)	16 (3)	3 (6)	13 (3)	0.26	
Birth year ≥ 2003, *n* (%)	43 (8)	19 (38)	24 (5)	< 0.001*	19.43, 47.93
Liver abscess, *n* (%)	87 (17)	10 (20)	77 (17)	0.59	
Aspergillus infection, *n* (%)	158 (31)	16 (32)	142 (31)	0.88	
Granulomatous gastrointestinal disease, *n* (%)	111 (22)	26 (52)	85 (19)	< 0.001*	18.50, 45.91
Chronic pulmonary disease, *n* (%)	26 (5)	5 (10)	21 (5)	0.14	
Interferon-gamma treatment, *n* (%)	206 (41)	18 (36)	188 (41)	0.47	
Mortality, *n* (%)	75 (15)	6 (12)	69 (15)	0.56	
Year of diagnosis, median (range)	1989 (1953–2016)	2001 (1970–2012)	1988 (1953–2016)	< 0.001*	− 13.60, − 4.40
Age at the onset of symptoms in years, median (range)	2.0 (0.1–19.6)	1.5 (0.1–5.7)	2.0 (0.1–19.6)	0.16	
Age at diagnosis in years, median (range)	2.0 (0.1–34.2)	1.6 (0.1–17.0)	2.0 (0.1–34.2)	0.79	
Age at the last follow-up in years, median (range)	14.0 (1.0–53.0)	15.5 (4.0–38.0)	14.0 (1.0–53.0)	0.19	
Follow-up time from diagnosis to the last visit in years, median (range)	9.1 (0–45.8)	13.3 (3.0–35.0)	8.8 (0–45.8)	0.043*	− 7.62, − 2.01

HCT allogeneic hematopoietic stem cell transplant, *CI* confidence interval

† Proportions were compared by the chi-square test, and medians were compared by the Mann-Whitney *U* test

*Statistically significant at $p \leq 0.05$

(ages 2.6 years and 23.1 years at T_0) following transplants from matched unrelated donors (MUDs). Both had histories of multiple severe infections and granulomatous gastrointestinal disease, with the adult patient also suffering numerous infections post-transplant (candidemia, *Legionella* peritonitis, CMV colitis, and BK cystitis). Two subjects (ages 4.8 years and 37.0 years at T_0) who received PBSC from MUDs following RIC died of respiratory failure 17 months and 2 weeks after transplant, respectively, the latter of whom had a hepatic abscess and *Nocardia* lung abscess pre-HSCT. One 18-year-old patient with liver abscess, esophagitis, and gastric outlet obstruction before transplant died of gastrointestinal hemorrhage 9 months post-HSCT (Table S2).

Five patients who died had documentation of severe infections or inflammatory disease prior to transplant (Table S2). No mortality was reported in patients who received stem cells from matched siblings, or bone marrow (BM) with RIC ($n = 6$) or minimal-intensity conditioning (MIC) ($n = 1$). Of the four patients who received UCB, all were alive at last follow-up.

Allogeneic HSCT Complications

Eleven patients developed GvHD, including acute ($n = 8$), chronic ($n = 2$), or acute and chronic ($n = 1$) disease. Of subjects with acute GvHD, seven received PBSC, and seven underwent non-myeloablative conditioning. Three cases of grade I and two cases of grade III disease were reported. Patients who developed chronic GvHD had a history of visceral abscess and/or granulomatous enterocolitis, two of whom were > 14 years old at T_0.

Three cases of graft failure using MUDs were reported; one patient underwent second HSCT 4 months after original transplant, and two patients were alive and well at $T + 3$ months and $T + 73$ months (Table S2). Seven patients received stem cell boost infusions 1–8 months post-HSCT, the majority of whom received PBSC ($n = 5$) from MUD ($n = 6$).

Infection Pre-HSCT and Post-HSCT

Infection episodes significantly declined post-HSCT in 18 subjects with greater than or equal to four infections pre-HSCT ($p < 0.001$ [95% CI = 0.2, 16.2]). No new infections were recorded > 24 months after T_0 (Fig. 2).

The mean number of severe infections accrued prior to transplant was lower for patients ≤ 14 years old at T_0 (0.95 ± 0.91) than for patients > 14 years old at T_0 (2.13 ± 2.00) ($p = 0.047$) (Table 2). However, the mean number of severe infections per CGD life year did not significantly differ between the younger (0.26 ± 0.35) and older (0.10 ± 0.10) transplant groups ($p = 0.084$).

Table 2 HSCT cohort demographics, compared by age at the first stem cell transplant

	Total ($n = 50$)	T_0 at ≤ 14 years old ($n = 28$)	T_0 at > 14 years old ($n = 22$)	p value†	95% CI
Median age at the onset of symptoms in years (range)	1.5 (0.1–5.7)	1.0 (0.1–5.7)	1.75 (0.5–4.0)	0.23	
Median age at diagnosis in years (range)	1.6 (0.1–17.0)	1.0 (0.2–3.5)	3.0 (0.1–17.0)	0.19	
Median age at transplant in years (range)	13.1 (0.6–37.3)	6.7 (0.6–14.0)	21.8 (15.0–37.3)	< 0.001*	161.72, 216.28
Mean number of severe infections pre-HSCT ± SD	1.27 ± 0.87	0.95 ± 0.91	2.13 ± 2.00	0.047*	0.33, 2.03
Clinical features, *n* (%)					
Male	47 (94)	25 (89)	22 (100)	0.16	
CYBB mutation	36 (72)	18 (64)	18 (82)	0.16	
Interferon gamma treatment	18 (36)	8 (29)	10 (45)	0.22	
Liver abscess	10 (20)	4 (14)	6 (27)	0.26	
Granulomatous enterocolitis	21 (42)	12 (43)	9 (41)	0.89	
Mortality	6 (12)	2 (7)	4 (18)	0.035*	0.80, 25.20
Stem cell donor, *n* (%)					
Matched unrelated	31 (62)	18 (64)	13 (59)	0.71	
Matched related	8 (16)	3 (11)	5 (23)	0.26	
Haploidentical	2 (4)	2 (7)	0 (0)	–	
Mismatched unrelated	2 (4)	2 (7)	0 (0)	–	
Graft, *n* (%)					
Peripheral blood stem cells	26 (52)	10 (36)	16 (73)	0.010*	9.14, 57.62
Bone marrow	14 (27)	11 (39)	3 (14)	0.047*	0.45, 46.00
Umbilical cord blood	4 (8)	4 (14)	0 (0)	–	
Conditioning regimen, *n* (%)					
Minimal intensity	5 (10)	3 (11)	2 (9)	0.85	
Reduced intensity	25 (50)	12 (43)	13 (59)	0.27	
Myeloablative	4 (8)	4 (14)	0 (0)	–	
Graft-versus-host disease, *n* (%)					
Acute	9 (18)	6 (21)	3 (15)	0.59	
Chronic	3 (6)	1 (4)	2 (9)	0.47	

T_0 is the time of the first stem cell transplant

HCT allogeneic hematopoietic stem cell transplant, *CI* confidence interval, *SD* standard deviation

† p value and 95% CI for mortality were estimated by the Kaplan-Meier method. Other variables were compared by the Mann-Whitney U test (median age of symptom onset, diagnosis, and transplant), Student's t test (mean number of severe infections pre-HSCT), or chi-square test (remainder)

*Statistically significant at $p \leq 0.05$

Granulomatous Disease Pre-HSCT and Post-HSCT

Seventeen HSCT patients (34%) had documentation of granulomatous disease prior to transplant (14 had insufficient record of temporal correlation with transplant). The most common manifestation was esophageal-gastrointestinal ($n = 15$), including three subjects with esophageal strictures and three subjects with gastrointestinal obstruction. Pulmonary ($n = 3$), urinary bladder ($n = 2$), cutaneous ($n = 2$), and ocular ($n = 1$) pathology was less common. Two adults with preexistent gastrointestinal or pulmonary granulomatous disease, in addition to multiple infections, died (Table S2). Two additional subjects did not have post-transplant data regarding comorbidities available.

Eleven of the remaining 13 subjects had reduction in the record of granulomatous disease post-HSCT, with nine having no documentation of granulomata at the median post-transplant interval of 24 months (1–35 months). Two subjects had post-transplant decline in the number of cited granulomatous complications (one with resolution of colitis, but persistent lung disease, at 3-year follow-up; another with a resolution of esophageal strictures, but persistent enterocolitis, at 7-month follow-up).

Functional Performance Analysis

The mean performance score in non-HSCT patients declined with an increasing decade of life ($p < 0.001$) (Fig. 3; Table S3).

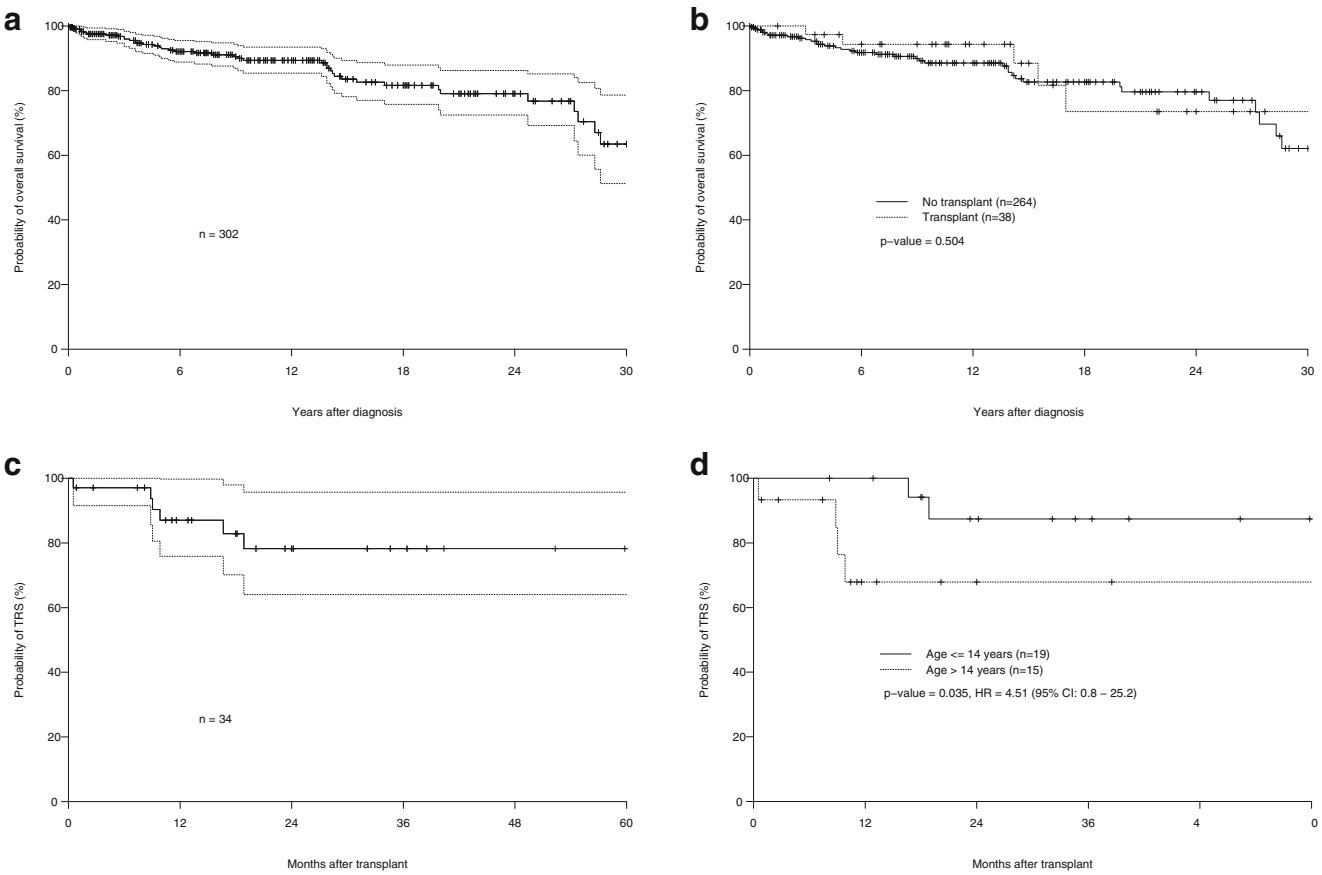

Fig. 1 Kaplan-Meier estimates of **a** post-diagnosis overall survival (OS) in all evaluable CGD patients (dashed lines indicate 95% confidence intervals (CI)) and **b** OS in patients treated with or without allogeneic hematopoietic stem cell transplant (HSCT). **c** Transplant-related survival (TRS) in evaluable HSCT patients (dashed lines indicate 95% CI). **d** TRS stratified by age at T_0, ≤ 14 years old v. > 14 years old

The mean score of 0–10-year-old patients (96.00 ± 6.32) was significantly higher than that of 21–30-year-old patients (86.95 ± 7.45) (p = 0.043), and the mean score of 11–20 year-old patients (90.63 ± 13.40) was higher than that of > 40 year-old patients (77.14 ± 9.51) (p = 0.016) (Fig. 3; Tables S3 and S4). The mean performance score for post-transplant patients did not change significantly based on age at assessment (p = 0.75) (Fig. 3; Table S5). The median age at transplant was 19.5 years (0.6–30.0 years), and the median time of evaluation was 23 months after T_0 (1.0–402.5 months) for post-HSCT subjects.

For living subjects ≥ 15 years old at last follow-up, the mean performance score was higher in post-HSCT (93.16 ± 6.71) versus non-HSCT (85.88 ± 9.50) patients (p = 0.0039). The frequency of disability was lower in post-transplant (11%) versus non-transplant (52%) subjects (p = 0.014) (Table 4). Genetic and evaluable clinical features of the HSCT group prior to transplant and the non-HSCT group were comparable (Table S6). Pulmonary insufficiency was the most commonly reported disability in non-transplant patients ≥ 15 years old (Table 4). Depression resolved post-HSCT in four of four patients with citation of this condition before HSCT. Approximately 17% of non-transplant patients had record of mood or cognitive disorders.

Discussion

This report details analysis of the largest North American CGD cohort reported at the time of authorship, spanning 63 years of diagnosis. Consequently, this data reflects evolving practice standards, and outcomes of allogeneic HSCT have improved considerably [30]. A mitigating factor is that of 50 transplanted patients, 36 underwent allogeneic HSCT between 2012 and 2016, and there was no significant difference in OS between patients transplanted from 1982 to 2011 versus those transplanted from 2012 to 2016 (p = 0.31).

Accomplishment of allogeneic HSCT before 15 years old was associated with improved TRS, estimated to be 90% after T + 18 months (Fig. 1d; Table 3). Six case series of predominantly bone marrow transplant (BMT) similarly reported 100% TRS in patients undergoing HSCT before 12 years old, with a median follow-up of 17–70 months post-HSCT [31–36]. Potential causes of reduced TRS in older patients include the accumulation of end-organ damage due to recurrent infection, granulomatous disease, or pharmacologic toxicity; increased incidence of hyperinflammatory events after adolescence [21]; reduced medication compliance [37–39]; or immune changes related to pubertal hormones [40–43].

Table 3 Cox regression models showing associations between clinical characteristics and mortality in all evaluable CGD patients (top) and transplanted patients (bottom)

Model covariates	Hazard ratio for death (95% CI)	*p* value
Multivariate analysis of overall survival ($n = 302$)		
HSCT (+/−)	1.26 (0.47, 3.35)	0.65
CYBB mutation (+/−)	6.25 (1.14, 33.33)	0.034*
Birth year (before v. during or after 2003)	1.51 (0.35, 6.46)	0.58
Liver abscess (+/−)	0.63 (0.28, 1.43)	0.27
Aspergillus infection (+/−)	1.11 (0.56, 2.23)	0.77
Granulomatous gastrointestinal disease (+/−)	0.54 (0.25, 1.17)	0.12
Chronic pulmonary disease (+/−)	0.10 (0.0060, 1.74)	0.11
Bivariate analyses of transplant-related survival ($n = 38$)		
Age at T_0 v.	1.10 (1.01, 1.21)	0.034*
Number of infections pre-HSCT (per infection increase)	0.85 (0.54, 1.34)	0.48
Age at T_0 v.	1.10(1.01, 1.20)	0.036*
Number of severe infections pre-HSCT (per infection increase)	0.84 (0.52, 1.37)	0.48
Age at T_0 v.	1.06 (0.93, 1.21)	0.38
Graft type (BM v. PBSC)	0.56 (0.040, 8.30)	0.67
Age at T_0 v.	1.11 (0.95, 1.30)	0.19
Conditioning regimen (MAC v. RIC/MIC)	0.11 (0.0030, 4.81)	0.26
Age at T_0 v.	1.14 (0.99, 1.30)	0.066
Birth year (before v. during or after 2003)	3.2 (0.18, 58.56)	0.43
Age at T_0 v.	1.06 (0.97, 1.17)	0.22
CYBB mutation (+/−)	0 (0, not available)	1.00

CI confidence interval, *HCT* allogeneic hematopoietic stem cell transplant, *BM* bone marrow, *PBSC* peripheral blood stem cells, *MAC* myeloablative conditioning, *RIC* reduced-intensity conditioning, *MIC* minimal-intensity conditioning

*Statistically significant at $p \leq 0.05$

The absence of independent association between preexisting severe infection or granulomatous disease and hazard of dying in this dataset (Table 3; Table S1) may relate to inadequate power, a multifactorial model of mortality, or the aforementioned additional factors. Because granulomatous disease typically increases in prevalence after adolescence [21], it is possible that median follow-up of 9 years did not capture the impact on survival. Examining the severity and distribution of granulomas

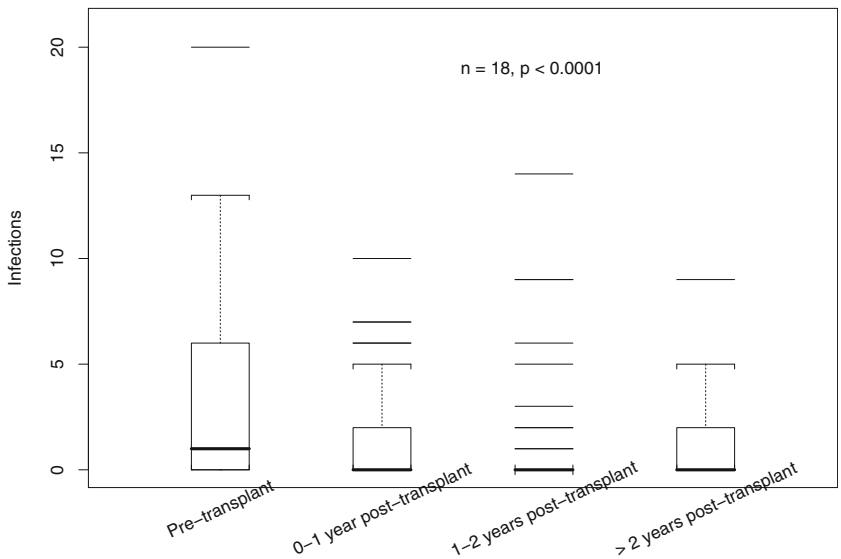

Fig. 2 Change in the incidence of infection after hematopoietic stem cell transplant (HSCT) in 18 patients with greater than or equal to four infections pre-HSCT, estimated by Poisson regression ($p < 0.001$)

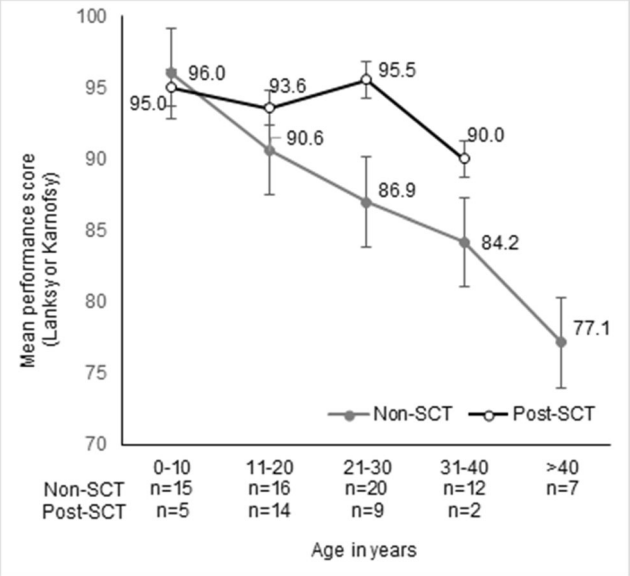

Fig. 3 Mean performance scores (with standard error) in non-hematopoietic stem cell transplant (HSCT) and post-HSCT patients, stratified by age at assessment and compared by one-way ANOVA

could help to identify phenotypes at enhanced fatality risk: for example, portal hypertension secondary to granulomatous disease has been associated with increased mortality [11, 12]. Additionally, granulomatous destruction of innate epithelial immunity may predispose patients to infection. It may be statistically challenging to determine whether infectious or sterile inflammation plays a larger role in mediating mortality.

When analyzed as a function of residual ROI synthesis, survivorship similarly diverged near the end of the second decade of life: patients producing < 2.3 nmol superoxide per 10^6 cells per h demonstrated a sharp decline in survival around 20 years of age [5]. This parallels the survivor distribution of *CYBB* mutants we estimated, in which OS fell below 80% 15 years after diagnosis (Fig. S3), with a median age of diagnosis of 1.4 years. We further observed accumulation of two severe infections by 14 years old in transplanted patients (Table 2), and restriction of TRM to patients with pharmacologically refractory or multiple severe infections is well documented [26, 31, 36, 44]. Collectively, this data suggests that in patients with severely abrogated ROI synthesis, accomplishment of definitive treatment before mid-adolescence may offer the greatest survival benefit, in part due to reduced preexisting infection.

Overall survival in the general cohort (Fig. 1a) was similar to European and Asian populations [16–21, 45]. No single infectious or hyperinflammatory comorbidity was independently associated with mortality risk (Table 3), though severity was not quantified, and this dataset reflects a broad timespan with heterogeneous treatment availability. Frequency of liver abscess (17%) (Table 1) was comparable to Italian and pediatric UK registries [19, 25].

OS did not differ between post-HSCT and non-HSCT subjects (Fig. 1b), including isolated analysis of *CYBB* mutants (Fig. S1). While the median year of diagnosis was lower in non-transplant patients (1988 v. 2001) (Table 1)—implicating reduced availability of advanced azole derivatives [45, 46]—neither *Aspergillus* infection nor advanced birth year (after 2002) was independently associated with mortality (Table 3; Table S1). The estimated OS distribution did not significantly differ between non-HSCT and post-HSCT subjects born in 2003–2016 (Fig. S2), though the relative youth of this cohort

Table 4 Performance score and disability in post-HSCT and non-HSCT subjects ≥ 15 years old at the last visit

	Post-HSCT ($n = 18$)	Non-HSCT ($n = 50$)	p value†	95% CI
Median age at assessment in years (range)	24.0 (15.0–34.0)	27.0 (15.0–53.0)	0.080	
Mean performance score ± SD (range)	93.16 ± 6.71 (70–100)	85.88 ± 9.50 (50–100)	0.0039*	2.41, 12.15
Frequency of disability (%)	2 (11)	26 (52)	0.014*	13.15, 58.22
	Partial, 2 (11)	**Partial, 24 (48)**	0.013*	9.27, 54.43
	Depression, 1	Pulmonary insufficiency, 8		
	Unspecified, 1	Colitis complications, 5		
		Cognitive deficits, 2		
		Vision impairment, 2		
		Gait abnormality, 1		
		End-stage renal disease, 1		
		Depression, 1		
		Anxiety, 1		
		Unspecified, 3		
	Full, 0 (0)	**Full, 2 (4)**	0.42	
		Pulmonary insufficiency and malabsorption, 1 each		
		Unspecified, 1		

HSCT allogeneic hematopoietic stem cell transplant, *CI* confidence interval

† Median ages at assessment were compared by the Mann-Whitney *U* test. Mean performance scores were compared by Student's *t* test. Disability frequencies were compared by chi-square tests

*Statistically significant at $p \leq 0.05$

limits the discrimination of long-term survival disparity. The median follow-up time of 9 years may be too short to discern an effect on overall survival. There was likely selection bias for patients with enhanced morbidity to undergo HSCT: the frequency of granulomatous gastrointestinal disease was higher in HSCT patients (Table 1). ROI production within the mutant *CYBB* cohort may have been variable [5].

In the UK, OS was similarly equivalent (90%) in non-HSCT and post-HSCT CGD patients [25]. High OS in this cohort may relate to young age at assessment (all subjects were < 17 years old) and at transplant (median 5.3 years, range 0.7–15.3 years) [25]. HSCT was associated with survival advantage in a Swedish cohort of 41 patients diagnosed in 1990–2012, in whom infection-related mortality in non-HCT subjects was 37%, and TRM was low (one of 14 transplanted patients who received cord blood from a mismatched donor died of GvHD, severe viral and bacterial infections, and colitis). This group is notable for a relatively low incidence of high-risk features pre-HCT (only half had repeated life-threatening infections or recalcitrant granulomatous disease) and preponderance of transplants before 16 years old [28].

Restricted longitudinal data (particularly for non-HSCT subjects) and incomplete documentation of supportive care are limitations of this registry, with approximately 60% of the cohort having evaluable survival data. The number of transplants performed and the severity of pre-transplantation disease may be underestimated. Single-encounter data capture for some non-HCT patients may not reflect current mortality. However, nearly two thirds of HCT patients were followed for ≥ 12 months post-transplant, with 38 (76%) having last follow-up in 2015–2016.

TRM is typically multifactorial, but advances in antimicrobials and early transplantation may augment the role that non-infectious etiologies play. Sterile inflammatory conditions and/or GvHD were documented in five of six transplant-related deaths (Table S2), similar to trials evaluating busulfan [32] and treosulfan [43]-based RIC for CGD in which 3/4 and 4/6 deaths, respectively, involved GvHD or graft failure. Innate immune system polymorphisms [47, 48], impaired efferocytosis [7, 8], and gastrointestinal mucosal inflammation [24] may predispose CGD patients to graft-versus-host responses. In spite of the notable contribution of GvHD to mortality in these studies, event-free survival (81–89%) and overall survival (91–93%) were high at the median post-transplant follow-up of 21–34 months. Concomitant infection also played a role in the majority of deaths [32, 44].

PBSCs were used more frequently in subjects > 14 years old at T_0 (Table 2) and non-significantly associated with GvHD (9 of 11 patients with GvHD received PBSC). As such, alternative grafts may be considered. No deaths were reported in USIDNET patients who received BM with RIC or MIC. Documentation of graft failure was low (6%) and comparable to other series (of primarily myeloablative BMT) illustrating high engraftment (89–100%), maintenance of full or mixed donor chimerism (often > 90%), and achievement of sustained neutrophilic oxidative burst in > 70% phagocytes at the median post-HSCT follow-up of 17–61 months [26, 31, 32, 34, 35]. Survival benefit can be retained with low donor chimerism due to the protective effect of small amounts of superoxide [5].

Patients who survived ≥ 12 months post-HSCT demonstrated a significant reduction in the incidence of infection (Fig. 2), congruent with prior reviews demonstrating no new infections 3–8 months post-HSCT [26, 32]. In a British pediatric cohort, post-HSCT survivors had a decreased frequency of infections, surgeries, and hospital admissions (0.15 episode per transplant year) relative to non-HCT children (0.71 episode per CGD year) [25].

Record of granulomatous disease also declined post-HSCT: eight of nine patients with steroid-dependent colitis prior to transplant did not have documentation of corticosteroid use for this indication after HCT. Sustained clinical remission of colitis after discontinuation of immunosuppression for GvHD prophylaxis [26, 31, 33, 34], improved pulmonary function [26], and catch-up growth [25, 26] have been described.

HSCT altered the natural history of performance score decline seen in non-HSCT subjects (Fig. 3; Tables S3–S5). Interpretation is guarded due to the small sample size and lack of longitudinal data in individual patients. However, the pre-HSCT and non-HSCT groups were genotypically and phenotypically comparable in terms of documented infectious and inflammatory sequelae (Table S6), indicating that functional status may have been similar before HSCT. Birth year was also similar in each age category for non- and post-transplant patients, suggesting equivalent supportive care availability. Improved scores on quality-of-life indices following HCT (corresponding to healthy population norms) have been reported in pediatric CGD patients [27].

Conclusions

In the USIDNET CGD cohort, overall survival did not differ between patients treated with or without allogeneic HSCT. Post-HSCT survivors had reduced infection incidence and higher functional performance scores than non-transplant patients. Transplant-related survival was elevated in patients undergoing HCT before 15 years old, who had fewer severe preexistent infections. Consider HCT prior to late adolescence in patients with severely diminished ROI synthesis, particularly if a matched sibling is available. Prospective studies are needed to evaluate long-term outcomes of contemporary CGD management, including gene therapy.

Acknowledgements The United States Immunodeficiency Network (USIDNET) is supported by a cooperative agreement, U24AI86837, from the National Institute of Allergy and Infectious Diseases (NIAID)/National Institute of Health (NIH), which has been awarded to the Immune Deficiency Foundation.

The authors would like to thank the USIDNET Steering Committee (Dr. Charlotte Cunningham-Rundles, Dr. Luigi Notarangelo, and Dr.

Jennifer Puck) and Marla Goldsmith (Registry Manager) for their contributions to this work.

Authorship Contributions All coauthors have reviewed this manuscript and have contributed in a substantive and intellectual manner to this work.

Funding The USIDNET is supported by a cooperative agreement (U24AI86837) from the National Institute of Allergy and Infectious Diseases (NIAID)/NIH, which has been awarded to the Immune Deficiency Foundation.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

Appendix

Table 5 Institutions and the number of CGD patients diagnosed in 1953–2016

Enrolling institution	Participants
Advocate Hope Children's Hospital	4
Children's Hospital of Michigan	5
Children's Hospital of Orange County	1
Children's National Medical Center	1
Children's Hospital of Philadelphia	17
Cincinnati Children's Hospital Medical Center	4
Duke Medical Center	2
Emory Children's Center	1
Immune Deficiency Foundation	344*
Levine Children's Hospital	2
Massachusetts General Hospital	1
Mayo Clinic	1
Memorial Healthcare Systems	3
Mount Sinai Medical Center	5
Nationwide Children's Hospital	1
National Institutes of Health	89
Seattle Children's Hospital	7
University of Iowa Hospital	3
University of California San Francisco	8
University of Utah	4
United States Immunodeficiency Network	4

*Refers to de-identified patients enrolled in the National Institute of Allergy and Infectious Disease chronic granulomatous disease registry, established prior to the inception of, and later integrated with, the United States Immunodeficiency Network Registry

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