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Outcome of chronic granulomatous disease - Conventional treatment vs stem cell transplantation

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Abstract

Background: Hematopoietic stem cell transplantation (HSCT) can cure chronic granulomatous disease (CGD), but it remains debated whether all conventionally treated CGD patients benefit from HSCT.

Methods: We retrospectively analyzed 104 conventionally treated CGD patients, of whom 50 patients underwent HSCT.

Results: On conventional treatment, seven patients (13%) died after a median time of 16.2 years (interquartile range [IQR] 7.0-18.0). Survival without severe complications was $10 \pm 3\%$ (mean $\pm$ SD) at the age of 20 years; 85% of patients developed at least one infection, 76% one non-infectious inflammation. After HSCT, 44 patients (88%) were alive at a median follow-up of 2.3 years (IQR 0.8-4.9): Six patients (12%) died from infections. Survival after HSCT was significantly better for patients transplanted ≤8 years ($96 \pm 4\%$) or for patients without active complications at HSCT (100%). Eight patients suffered from graft failure (16%); six (12%) developed acute graft-vs-host disease requiring systemic treatment. Conventionally treated patients developed events that required medical attention at a median frequency of 1.7 (IQR 0.8-3.2) events per year vs 0 (IQR 0.0-0.5) in patients beyond the first year post-HSCT. While most conventionally treated CGD patients failed to thrive, catch-up growth after HSCT in surviving patients reached the individual percentiles at the age of diagnosis of CGD.

Conclusion: Chronic granulomatous disease patients undergoing HSCT until 8 years of age show excellent survival, but young children need more intense conditioning to avoid graft rejection. Risks and benefits of HSCT for adolescents and adults must still be weighed carefully.

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1 | INTRODUCTION

Chronic granulomatous disease (CGD) is caused by mutations in genes coding for subunits or regulatory proteins of the NADPH oxidase complex, that is, X-linked mutations in *CYBB* or autosomal recessive mutations in *CYBA*, *NCF1*, *NCF2*, and *CYBC1*, that cause absent or severely reduced production of superoxide in all phagocytes.[1,2] Autosomal recessive mutations in *NCF4* cause p40^{phox} deficiency, a similar, but distinct disease.[3] Besides its antimicrobial effect, reactive oxygen intermediates have immunoregulatory functions: For example, NADPH oxidase is required for the activation of ataxia-telangiectasia-mutated (ATM) kinase.[4] NADPH-deficient phagocytes show autophagic dysfunction and increased production of IL-1β upon activation with LPS and an interferon signature.[5,6] Therefore, CGD patients are not only at increased risk for infections, but also for non-infectious inflammatory granuloma formation, in particular inflammatory bowel and chronic lung disease.[1,7]

Conventional treatment of CGD comprises antibacterial and antifungal prophylaxis with cotrimoxazole and azoles, as well as immunosuppressive therapy.[7] Although prophylaxis has strongly decreased mortality, infections still occur at 0.26-0.64 per patient-year[8,9] with a cumulative lifetime risk for aspergillosis of 20%-40%, remaining the leading cause of death. In retrospective studies, the median lifespan of conventionally treated CGD patients is 30-40 years,[8] presumably dependent on the residual activity of the NADPH oxidase.[10] Immunosuppressive therapy, including long-term steroids, further increases the risk for infections and failure to thrive.[7] Consequently, quality of life, academic, and professional achievements are impaired on conventional treatment.[11,12] In contrast, allogenic hematopoietic stem cell transplantation (HSCT) potentially cures CGD. Because transplantation-related mortality was originally at 15%-50%, HSCT was used as salvage therapy for patients with recurrent infections or refractory inflammation.[13,14] Improved human leukocyte antigen matching (HLA) and fludarabine-based reduced-toxicity conditioning decreased treatment-related morbidity and mortality,

> **Key Message**
>
> Patients with chronic granulomatous disease (CGD) almost certainly benefit from allogenic hematopoietic stem cell transplantation (HSCT) from a human leukocyte antigen (HLA) matched donor, if performed before 8 years of age. Young children need more intense conditioning for stable engraftment. However, overall survival post-HSCT may be closer to approx. 85% (as opposed to >95% as previously reported). Risks and benefits of HSCT for adolescents and adults must still be weighed carefully.

apparently regardless of preexisting conditions. So, is current allogenic HSCT about to become the treatment of choice for CGD patients?[15-17]

2 | METHODS

2.1 | Recruitment of patients and participating centers

Chronic granulomatous disease patients, born after the 01 January 1980 and treated for at least 3 months with conventional treatment, were eligible. The diagnosis of CGD had to be established by two tests for production of superoxide in neutrophils and monocytes. By reviewing patient lists from the European Society of Immunodeficiency (ESID) and the Centre de Référence des Déficits Immunitaires Héréditaires (CEREDIH) registry, 124 potentially eligible patients were identified in six centers for immunodeficiency in France and Germany: 50 in Paris, 23 in Munich, 22 in Berlin, 10 in Dresden, 10 in Hannover, and nine in Freiburg. Approvals were obtained from the ethics committees of the Charité, ESID, and CEREDIH. Patients or parents gave informed consent for the study and/or for participation in the ESID/CEREDIH registry.
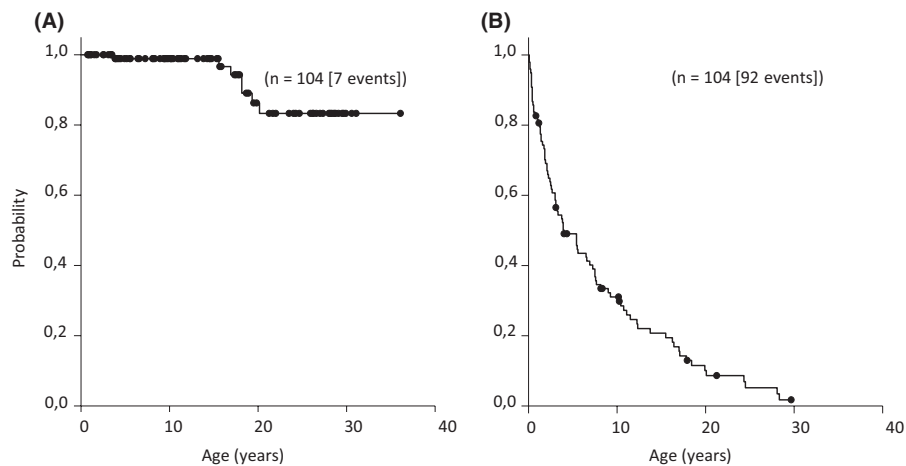
FIGURE 1 A, Probability estimates for overall survival and B, severe complication-free survival of all CGD patients plotted by age in years. Indicated are group sizes [and number of events]

2.2 | Data collection

Data were retrospectively collected at onsite visits in the centers between May 2016 and September 2017. Definitions on collected data are summarized (Table S1). Overall survival (OS) and *severe complication*-free survival were determined for conventionally treated patients and after HSCT, respectively. Patients undergoing HSCT were analyzed for event-free (EFS), that is, engrafted survival. A *severe complication* was defined as a proven or probable fungal infection, disseminated BCGitis, other life-threatening infections, non-infectious inflammation requiring systemic immunosuppressive therapy, organ failure, organ resection, or death. In transplanted patients, graft-vs-host disease (GVHD) requiring systemic therapy, that is, acute GVHD grade ≥II as defined by Glucksberg et al[18] or extended chronic GVHD,[19] and graft failure were also considered severe complications. Besides severe complications, all infections, inflammatory events, hospitalizations, and operations regardless of their severity were termed *events requiring medical attention* and calculated per treatment life-year. Weight and height were documented and z-scores calculated.

2.3 | Statistical analysis

Statistical analysis was performed using SigmaPlot version 11.0 (Systat Inc). Comparisons of categorical data were compared by using the Fisher exact test and continuous data by using the Mann-Whitney rank-sum test. Survival data were calculated by the Kaplan-Meier method and comparisons done by the log-rank method.

3 | RESULTS

3.1 | CGD cohort

Of 124 patients identified, 20 patients were excluded for incomplete records, non-acceptance to participate, or death immediately after

diagnosis. A total of 104 patients remained, 12 females and 92 males. While 54 patients continued conventional treatment, 50 received HSCT on physician's discretion after a median interval on conventional treatment of 3.2 years (interquartile range [IQR] 0.8-8.9). Reasons were usually severe complications at a young age and donor availability. For direct comparisons between groups, four more patients were excluded from the HSCT group to provide a minimum of 6 months of follow-up after HSCT. For detailed characteristics, see Table S2.

3.2 | Patients on conventional treatment

Median age of all 104 CGD patients at diagnosis was 2.2 years (IQR 0.5-5.8) and median follow-up was 9.3 years (IQR 2.4-16.8) (Table S2). On conventional treatment, seven patients (13%) died after a median time of 16.2 years (IQR 7.0-18.0), six from infections and one from non-infectious inflammation. At 20 y/a, estimated OS was 86 ± 5% (mean ± SD) and severe complication-free survival was 10 ± 3% (Figure 1; compare also Figure S1). Ninety-two patients (88%) suffered from at least one severe complication: 51 developed a bacterial, 44 a fungal or a disseminated BCG infection, 51 colitis, and 20 an inflammatory lung disease. On conventional treatment, infections occurred in 88 patients (85%) at a median frequency of 5 per patient (IQR 1-9), mostly affecting the skin and the lung (Figure 2). Identified pathogens are shown in Figure S2. Non-infectious inflammatory episodes developed in 79 patients (76%) at a median frequency of 2 per patient (IQR 1-7), mostly affecting the gastrointestinal tract. Seventy-four patients (71%) received at least once immunosuppression; 61 (59%) needed immunosuppression for more than 3 months.

3.3 | Patients after allogeneic HSCT

Fifty patients underwent allogeneic HSCT at a median of 5.6 y/a (IQR 3.4-11.8). Transplant details are summarized (Table S3). Until the end of 2010, 9 of 13 patients (69%) received conventional myeloablative
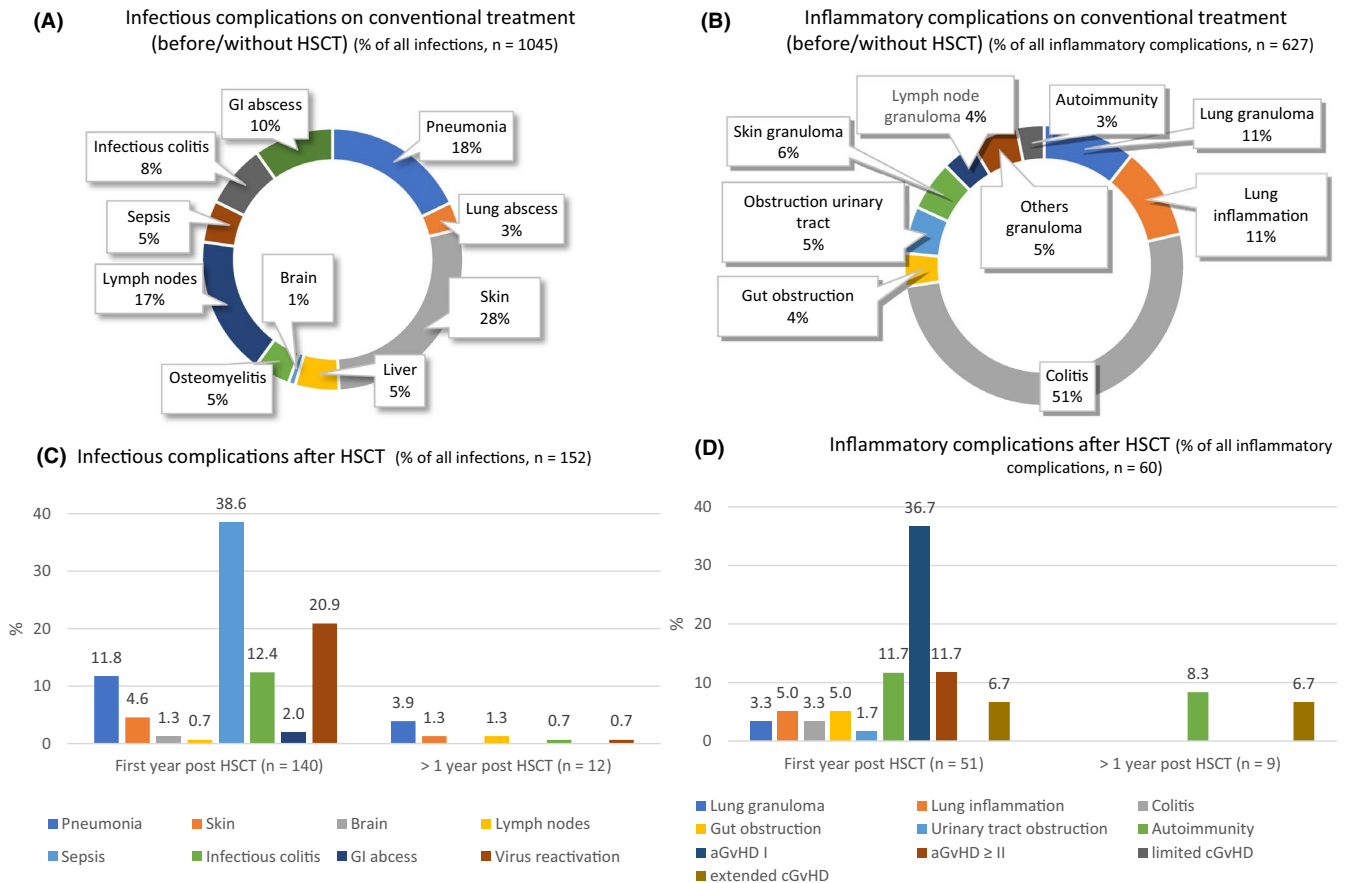
FIGURE 2 Relative frequency of infectious and inflammatory complications for all patients on conventional treatment (A, B) or after stem cell transplantation (C, D). Due to multiple events, total number of complications exceeds number of patients. CT, conventional treatment; HSCT, hematopoietic stem cell transplantation; GI, gastrointestinal; aGVHD, acute graft-vs-host disease; cGVHD, chronic GVHD

conditioning or were transplanted from a matched related donor, respectively. Thereafter, 29 of 37 patients, respectively, received an unrelated transplant or a reduced-toxicity regimen ($P = .005$). Forty-four patients in the HSCT group are alive at a median follow-up of 2.3 years (IQR 0.8-4.9) with an estimated OS of $86 \pm 6\%$ and an EFS of $73 \pm 7\%$ (Figure 3). Six patients died from proven or suspected infections, in 5 of the lungs. Four of these patients had undergone HSCT with an active infection which progressed during transplantation and aggravated by either graft failure (n = 2) or chronic GVHD (n = 1). The two others had an active inflammatory colitis at time of HSCT and died from newly acquired invasive infections associated with chronic GVHD. Eight patients (14%) suffered from graft failure (Figure S3): Altogether five patients had received a busulfan-based conditioning until the age of 4 years and 2 out of 3 who rejected at an older age a reduced-toxicity regimen with busulfan from a 9/10 HLA-matched donor resulting in a 4.3-fold elevated relative risk of graft failure in these patients ($P = .021$). After graft failure, six received a second donation of whom 5 survived. Acute GVHD grade ≥ II requiring systemic therapy was encountered in six patients (12%) (Figure S3) and extended chronic GVHD in 4 (8%).

A total of 140 of 152 infectious complications (92%) (of events requiring medical attention) occurred within the first year after

HSCT (Figure 2C). Eighteen patients had symptomatic virus reactivation requiring therapy (Figure S2), resolving within the first year in all but one patient with persisting adenovirus colitis associated with GVHD. Seven patients had infections after the first year: Three patients developed non-severe pneumonia, two others associated with chronic GVHD, and one a lymph node infection, later diagnosed as lupus erythematodes. Another patient with a history of severe colitis was hospitalized for infectious enteritis. Most inflammatory complications (85%) (of events requiring medical attention) occurred within the first year after HSCT as well (Figure 2). Only four patients experienced such events later: Two had extended chronic GVHD and 2 developed lupus or Hashimoto thyroiditis.

Patients undergoing HSCT with an active severe complication had an inferior survival (OS $75 \pm 9\%$ vs 100%) (Figure 3). Survival was also impaired in patients transplanted above 8 y/a (OS $70 \pm 12\%$ vs $96 \pm 4\%$). Similar differences were seen for patients with more than 5 years on conventional treatment before HSCT (OS $67 \pm 12\%$ vs $97 \pm 3\%$; $P = .018$). Neither conditioning regime nor donor source impacted survival. For engraftment, HLA matching was crucial: EFS after a 9/10 HLA-matched transplant was $43 \pm 19\%$ in contrast to $80 \pm 7\%$ after a 10/10 HLA-match ($P = .014$). In addition, EFS for
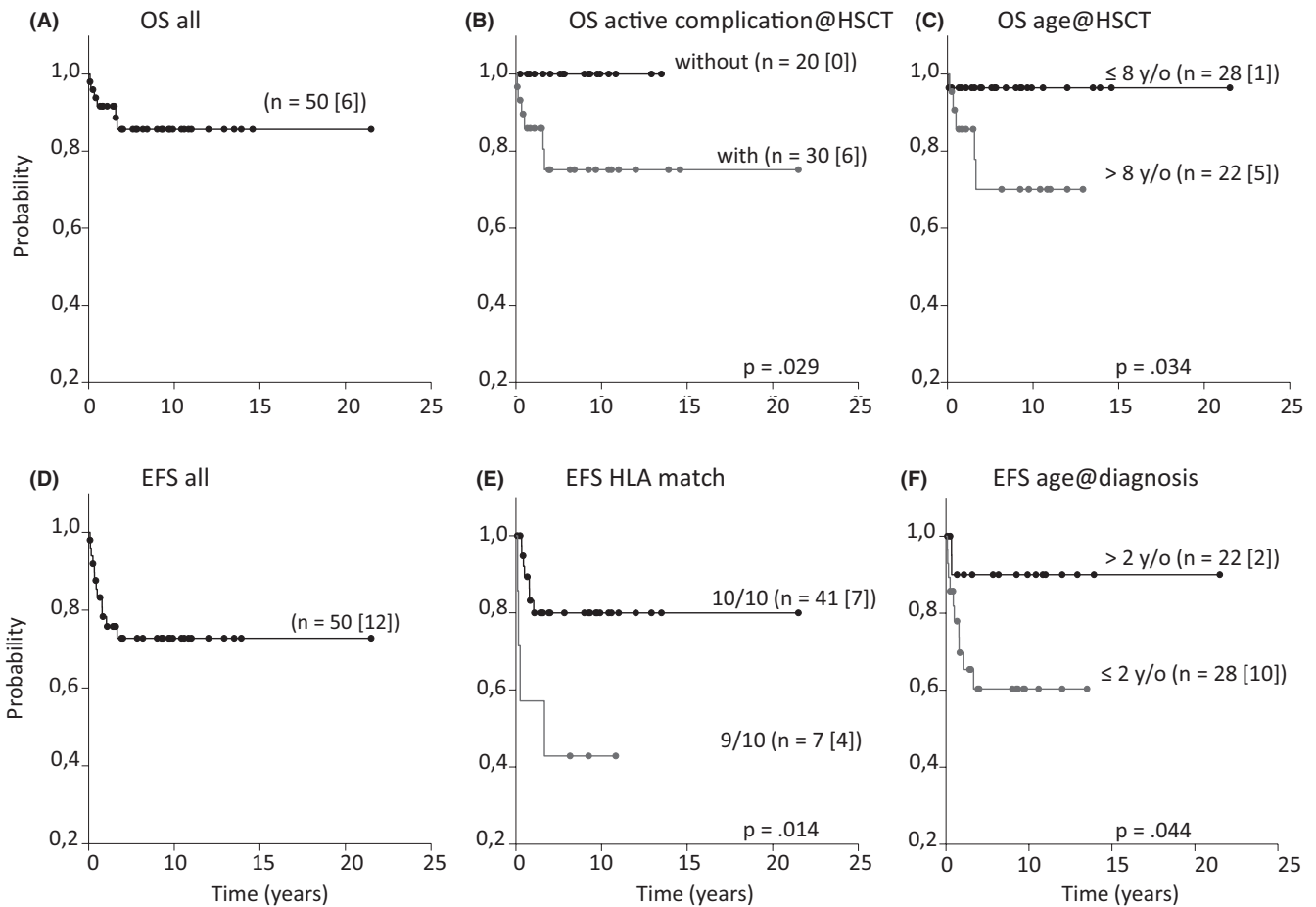
FIGURE 3 Top: Probability estimates for overall survival (OS) after HSCT (A) of entire cohort. OS stratified by (B) active complications in patients at time of transplant or (C) by age in years at transplantation. Bottom: Probability estimates for event-free survival (EFS) after HSCT (D) of entire cohort. EFS stratified by (E) donor match or (F) age in years of patients at diagnosis. Indicated are group sizes [and number of events]

patients diagnosed after 2 y/a (90 ± 7%) was superior to patients diagnosed before (60 ± 10%) (P = .044) (Figure 3).

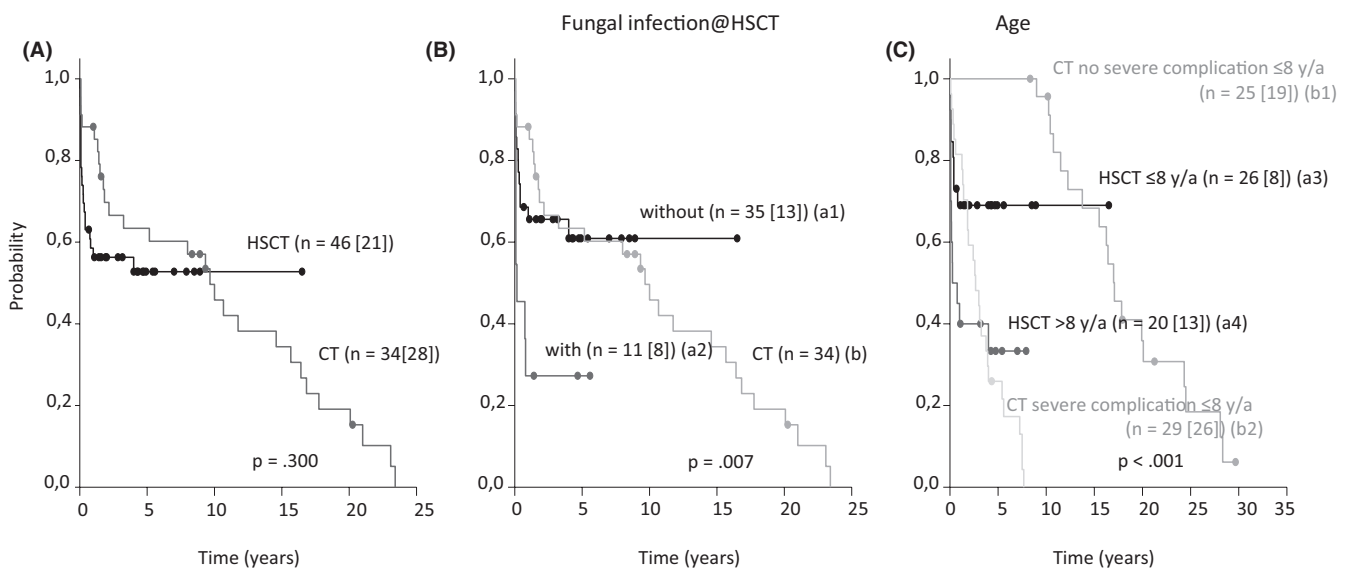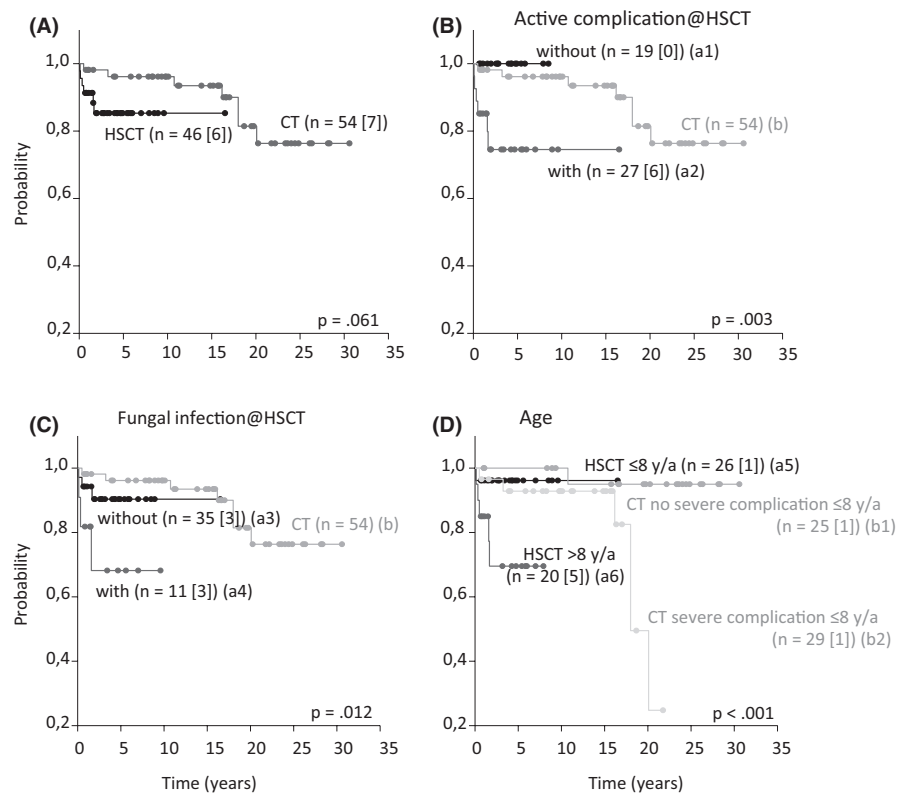## 3.4 | Comparison between conventionally treated and HSCT patients

In the conventionally treated group (n = 54), median age at diagnosis was 2.9 years (IQR 0.5-8.2), age at first severe complication was 5.5 years (IQR 1.8-14.2), and 20 patients (37%) developed their first severe complication before or at diagnosis. In the HSCT group with minimum follow-up of 6 months (n = 46), median age at diagnosis was 1.6 years (IQR 0.5-3.8), age at first severe complication was 1.8 years (IQR 0.4-5.4) (P = .002), and 31 patients (67%) developed their first severe complication before or at diagnosis. Before 2011, 38 of 46 (83%) conventionally treated patients had developed their first severe complication at a median age of 8.0 years (IQR 1.8-17.1) In contrast, all HSCT patients transplanted before 2011 had developed a severe complication on conventional treatment at a median age of 2.5 years (IQR 0.9-4.4) (P = .024). After 2015, transplant practice had changed: five of 13 (38%) transplanted patients had not

experienced a severe complication before HSCT in contrast to only one out of 33 (3%) in earlier years (P = .006).

For the entire cohort, survival after HSCT was not clearly superior to conventional treatment (Figure 4). However, survival rates of patients transplanted without active complications (OS 100%), particularly, without fungal infections (OS 90 ± 5%), were superior to the ones transplanted with active complications (OS 75 ± 9%) or with fungal infections (OS 68 ± 16%) and to conventionally treated patients. Stratifying for age revealed also a superior survival of patients transplanted until 8 y/a (96 ± 4%) and of conventionally treated patients who did not develop severe complications until 8 y/a (95 ± 5%). The latter group had a significantly better outcome than patients who were transplanted after 8 y/a (OS 70 ± 12%) and conventionally treated patients who experienced their first severe complication until this age (OS 25 ± 20%) (Figure 4).

While conventionally treated patients continuously developed severe complications over time, only eight of 36 HSCT patients (22%) developed one after the first year post-HSCT, which subsequently resolved in all but one (3%) (Figure 5). Etiology of these late complications was secondary graft failure in four patients, chronic GVHD in two, and VZV meningitis as well as autoimmune disease

FIGURE 4 Probability estimates for overall survival (OS) in patients after stem cell transplantation (HSCT) in comparison with conventional treatment (CT). (A) OS of entire HSCT vs conventionally treated cohort. (B) OS after HSCT stratified by active complications at time of transplantation in comparison with entire conventionally treated cohort. (C) OS after HSCT stratified by active fungal infection at time of transplantation in comparison to entire conventionally treated cohort. (D) OS after HSCT stratified by age in years at HSCT in comparison with conventionally treated patients stratified by age in years of first severe complication. Indicated are group sizes [and number of events]. Time line refers to time post-transplant or on conventional treatment. Significant differences in pairwise comparisons with overall $P < .05$: (B) b vs a2, (C) b vs a4, (D) b1 vs a6, b1 vs b2

FIGURE 5 Probability estimates for severe complication-free survival (CFS) in patients after stem cell transplantation (HSCT) in comparison with conventional treatment (CT). (A) CFS of entire HSCT cohort vs conventionally treated patients who did not experience any severe complication until start of conventional treatment. (B) CFS after HSCT stratified by active fungal infection at time of transplantation in comparison with conventionally treated cohort. (C) CFS after HSCT stratified by age in years at HSCT in comparison with conventionally treated patients stratified by age in years of first severe complication. Indicated are group sizes [and number of events]. Time line refers to time post-transplant or on conventional treatment. Significant differences in pairwise comparisons with overall $P < .05$: (B) a1 vs a2, b vs a2, (C) b1 vs b2, b1 vs a4, a3 vs b2

in one patient, respectively. Two of the graft failures were associated with very young age; all other late complications were either associated with active infection (n = 4) or inflammation (n = 2) at HSCT (Table S3). Patients undergoing HSCT without an active

fungal infection showed a superior severe complication-free survival (61 ± 9%) than patients with fungal infection (27 ± 13%) or conventionally treated patients (0%). Moreover, patients transplanted until 8 y/a had a better severe complication-free survival (69 ± 9%)
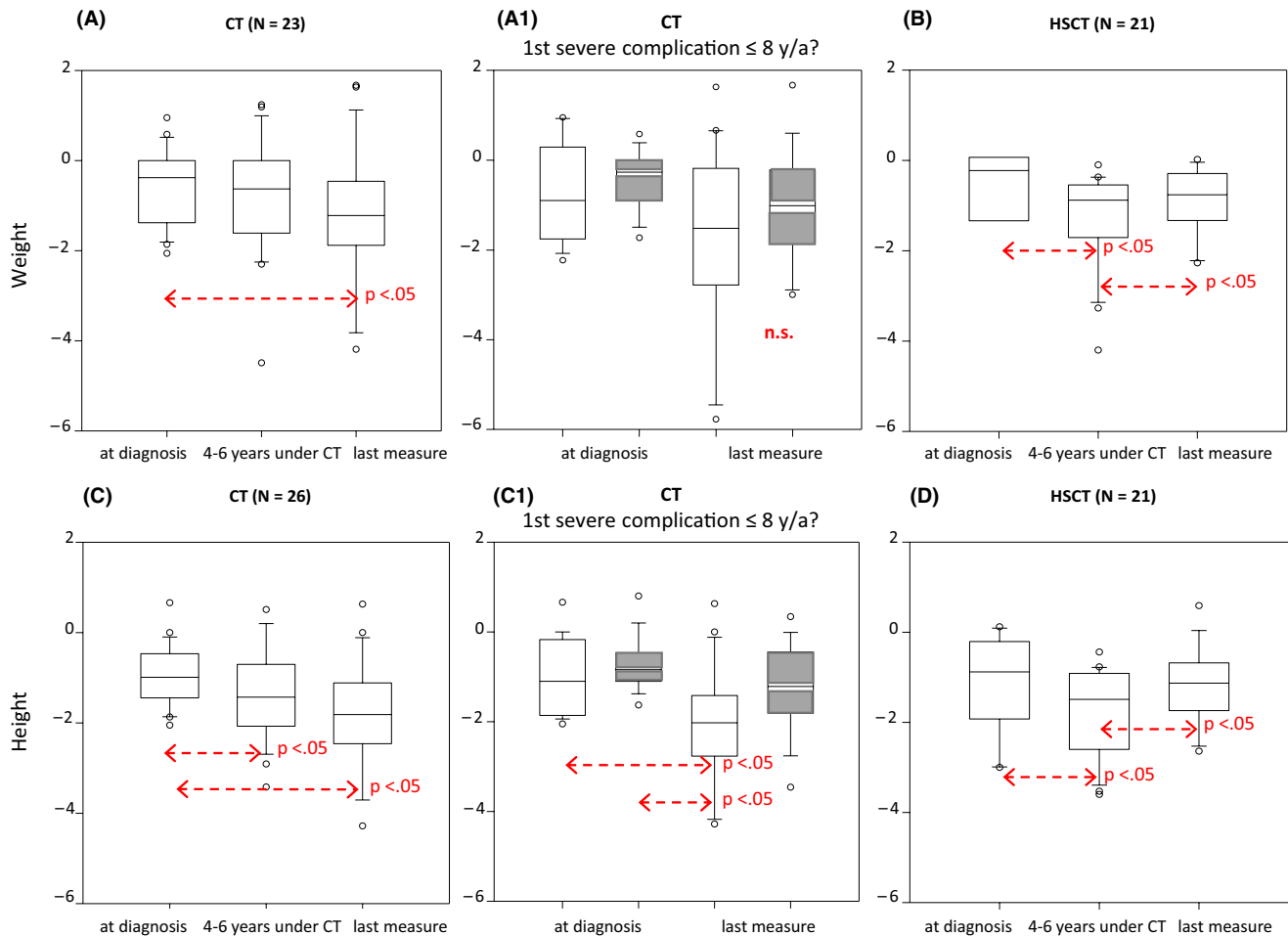
FIGURE 6 Z-scores for weight (top panel [A, A1, and B]) and height (bottom [C, C1, and D]) conventional treatment (CT [A, A1 and C, C1]) in comparison with transplanted patients (HSCT [B and D]). Analyzed were all conventionally treated patients of whom data were available at diagnosis, 4-6 y under conventional treatment, and minimum 2 y later. In HSCT patients, data at diagnosis, at time of transplant, and minimum 2 y after successful engraftment were compared. Additionally, Z-scores of conventionally treated patients who developed their first severe complication before the age of 8 y (white) were compared to other conventionally treated patients who did not (gray) (A1, C1). Illustrated are box plots with median, 25th and 75th percentile. Significant differences in pairwise comparisons with overall $P < .05$ are indicated

than patients transplanted thereafter (33 ± 11%) or conventionally treated patients with a first severe complication until 8 y/a (0%) (Figure 5).

Patients who remained on conventional treatment developed events that required medical attention at a median frequency of 1.7 per life-year, whereas patients who proceeded to HSCT had developed 3.4 of such events on conventional treatment. In the first year after HSCT, patients suffered from 7.0 events that required medical attention per HSCT life-year, but long-time survivors suffered from 0 such events during subsequent HSCT life-years ($P < .05$) (Table S4). Immunosuppression stopped in 40 patients (87%) within the first year after HSCT.

Z-scores for height and weight revealed that most conventionally treated patients increasingly failed to gain weight (median Z-score at diagnosis -0.35 [IQR −1.44-0.07] vs at last measurement −1.17 [IQR −1.87-−0.21]) and to grow (height at diagnosis −0.90 [IQR −1.21-−0.38] vs at last measurement −1.59 [IQR −2.35-−1.10]). Growth

was particularly impaired in conventionally treated patients with a first severe complication until 8 y/a. In the HSCT group, patients also failed to thrive between diagnosis and HSCT, but showed catch-up growth after successful HSCT: weight (at HSCT −0.88 [IQR −1.52-0.58] vs minimum 2 years post-HSCT −0.76 [IQR −1.32-−0.31]) and height (−1.49, IQR [−2.58-0.92] vs −1.13 [IQR −1.66-−0.70]) increased post-transplant to values as at diagnosis (Figure 6).

4 | DISCUSSION

Our study is the largest European study that compares the outcome of CGD patients on conventional treatment with those receiving HSCT. We retrospectively analyzed data from six centers in France and Germany, which follow up infants, children, adolescents, and adults. All patients were initially on conventional treatment; 50/104 subsequently underwent HSCT. In addition to standard end-points

of HSCT (OS, EFS), we also described severe complication-free survival and events which required medical attention. This allows a realistic description of risks and benefits for both ways to treat CGD. 85% of patients in our cohort developed at least one infection on conventional treatment, especially pneumonia and skin infections, whereas inflammatory complications were observed in 76%, comparable to previous reports.[7,12] We were unable to identify a subgroup with favorable prognosis on conventional treatment. Deleterious consequences of infections and non-infectious inflammation are mirrored by severe failure to thrive in most conventionally treated patients in our cohort, as reported previously.[9] Therefore, despite elaborate prophylaxis, CGD remains a potentially devastating disease that considerably hampers the quality of life and justifies allogenic HSCT as ultimate cure.[11,20]

Several studies compared the prognosis of CGD patients treated conventionally to those with HSCT. While a Swedish study on 41 patients reported a superior outcome of HSCT (93% vs 74% survival), other studies, including ours, fail to describe a clearly better survival after HSCT with survival rates ranging from 76% to 90% in both cohorts.[9,21-23] The result of our study is at least in part influenced by the fact that patients in the HSCT cohort generally showed a more severe course of chronic granulomatous disease than those patients who stayed on conventional therapy. However, UK, US, and our data indicate a significant reduction of infectious episodes and catch-up growth after HSCT.[9,23] In addition, due to the retrospective design of some studies and supposingly less rigorous follow-up of conventionally treated patients in comparison with HSCT patient, some deaths among conventionally treated patients may have been missed. Over the last decade, transplant series reported survival rates in CGD patients after matched donor transplantation of 83%-96%.[9,15,16,21-25] Although some studies emphasize a good tolerability of HSCT even in older patients after recurrent infections,[15,16] we and others showed that in particular patients younger than 5-14 y/a and without active complications at HSCT had an excellent outcome.[23-25] Therefore, all young CGD patients with a ≥9/10 HLA-matched available donor should be considered for HSCT.

An OS of 96% and 90% as well as an EFS of 91% and 81% reported for busulfan- or treosulfan-containing reduced-toxicity protocols, respectively, is unsurpassed for HSCT cohorts (Table S5), most likely indicating the unrivaled expertise of CGD transplant centers that performed these pilot studies.[15,16] Further, we, as well as others, did neither detect improvement for HSCT patients nor notice superior outcome after reduced-toxicity conditioning compared to conventional myeloablative conditioning.[23,25] In our series, this may be due to the fact that in participating centers early transplants before 2011 were primarily offered to carefully selected patients with a matched sibling donor, while the introduction of reduced-toxicity regimen gave rise to a less restrictive transplant approach. Especially with some reduced-toxicity regimens, graft failure rates are high.[22,26] In CGD, conditioning has to remain sufficiently myeloablative to achieve a predominant myeloid donor chimerism. The relatively low EFS in our cohort is also due to a high graft failure rate in younger children after busulfan-containing conditioning. This observation prompted some of us to increase the targeted busulfan to higher doses than originally recommended in the study by Güngör et al which comprised significantly less children younger 4 y/a than our cohort.[15]

So, general recommendations based on the Güngör-study have to be considered with some caution.[15] Our data and the cumulative experience of others suggest that allogenic HSCT from a matched donor is particularly worth to be considered for young CGD patients.[23-25] In contrast, conventionally treated patients who did not suffer from any severe complication before 8 y/a showed a better survival than patients who underwent HSCT after 8 y/a in our study. Moreover, in contrast to other conventionally treated patients, patients who had not suffered from any severe complication until 8 y/a hardly displayed failure to thrive. Hence, risks and benefits of HSCT for adolescents and adults must, beyond disposability of a matched donor, consider the individual clinical course. So, long-term absence of complications such as aspergillosis or colitis may be a better reason for a continuous watch-and-wait strategy than residual production of superoxide at diagnosis.[10] For patients without a matched donor, haploidentical HSCT or gene therapy may offer alternatives.[27-30] Long-term prospective studies to describe overall and severe complication-free survival as well as quality of life for both, conventionally treated and HSCT patients, are an unmet need.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

AUTHOR CONTRIBUTION

Cinzia Dedieu: Conceptualization (lead); Data curation (lead); Formal analysis (supporting); Investigation (lead); Methodology (supporting); Project administration (lead); Validation (equal); Visualization (supporting); Writing-original draft (supporting); Writing-review & editing (supporting). **Michael Albert:** Data curation (supporting); Investigation (supporting); Writing-original draft (supporting). **Nizar Mahlaoui:** Data curation (supporting); Investigation (supporting); Writing-original draft (supporting). **Fabian Hauck:** Data curation (supporting); Investigation (supporting); Writing-original draft (supporting). **Christian Hedrich:** Data curation (supporting);

Investigation (supporting); Writing-original draft (supporting). **Ulrich Baumann:** Data curation (supporting); Investigation (supporting); Writing-original draft (supporting). **Klaus Warnatz:** Data curation (supporting); Investigation (supporting); Writing-original draft (supporting). **Joachim Roesler:** Data curation (supporting); Investigation (supporting). **Carsten Speckmann:** Investigation (supporting). **Johannes Schulte:** Data curation (supporting); Investigation (supporting); Writing-original draft (supporting). **Alain Fischer:** Data curation (supporting); Investigation (supporting); Writing-original draft (supporting). **Stephane Blanche:** Data curation (supporting); Investigation (supporting); Writing-original draft (supporting). **Horst von Bernuth:** Conceptualization (lead); Formal analysis (supporting); Investigation (supporting); Methodology (lead); Project administration (lead); Supervision (lead); Validation (equal); Writing-original draft (lead); Writing-review & editing (lead). **Jörn-Sven Kühl:** Data curation (equal); Formal analysis (lead); Investigation (equal); Methodology (lead); Validation (lead); Visualization (lead); Writing-original draft (supporting); Writing-review & editing (lead).

ETHICAL APPROVAL

PEER REVIEW

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.