Granulocyte Transfusions in Patients with Chronic Granulomatous Disease Undergoing Hematopoietic Cell Transplantation or Gene Therapy

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Abstract
Granulocyte transfusions are sometimes used as adjunctive therapy for the treatment of infection in patients with chronic granulomatous disease (CGD). However, granulocyte transfusions can be associated with a high rate of alloimmunization, and their role in CGD patients undergoing hematopoietic cell transplantation (HCT) or gene therapy (GT) is unknown. We identified 27 patients with CGD who received granulocyte transfusions pre- (within 6 months) and/or post-HCT or GT in a retrospective survey. Twelve patients received granulocyte transfusions as a bridge to cellular therapy. Six (50%) of these patients had a complete or partial response. However, six of 10 (60%) patients for whom testing was performed developed anti-HLA antibodies, and three of the patients also had severe immune-mediated cytopenia within the first 100 days post-HCT or GT. Fifteen patients received granulocyte transfusions post-HCT only. HLA antibodies were not checked for any of these 15 patients, but there were no cases of early immune-mediated cytopenia. Out of 25 patients who underwent HCT, there were 5 (20%) cases of primary graft failure. Three of the patients with primary graft failure had received granulocyte transfusions pre-HCT and were subsequently found to have anti-HLA antibodies. In this small cohort of patients with CGD, granulocyte transfusions pre-HCT or GT were associated with high rates of alloimmunization, primary graft failure, and early severe immune-mediated cytopenia post-HCT or GT. Granulocyte transfusions post-HCT do not appear to confer an increased risk of graft failure.

Keywords Granulocyte transfusions · Chronic granulomatous disease · Alloimmunization · Hematopoietic cell transplantation · Graft failure

Introduction
Granulocyte transfusions have previously been shown to be a safe adjunctive therapy for the treatment of severe infection in patients with chronic granulomatous disease (CGD) [1]. However, granulocyte transfusions can be associated with a high rate of alloimmunization [2, 3], and as such, their use may adversely affect patients who subsequently undergo allogeneic hematopoietic cell transplantation (HCT) or gene therapy (GT). Furthermore, the efficacy of granulocyte transfusions peri-HCT and GT remains incompletely elucidated regardless of the patient population and indication for granulocyte transfusions.

Several studies have reported the safe use of granulocyte transfusions in patients with hematologic malignancy in the pre- and post-HCT setting [4–7]. However, studies with matched control groups and randomized controlled trials have not found a survival benefit in patients with neutropenia from chemotherapy or HCT and active infection [8, 9]. A Cochrane review in 2018 by Estcourt et al. [10] also found no difference in all-cause mortality or mortality due to infection between patients who did or did not receive prophylactic granulocytes post-HCT. Importantly, Price et al. [11]...
reported a lower rate of alloimmunization with granulocyte transfusions than that reported in CGD patients, possibly due to the more immunosuppressed state of patients with hematologic malignancy receiving chemotherapy. There have been only a few case reports in CGD patients on the successful use of granulocyte transfusions to treat infection pre- and/or post-HCT [12–14].

The role of granulocyte transfusions in patients with CGD undergoing HCT or GT has not been explored in depth. We conducted a retrospective survey through the Primary Immune Deficiency Treatment Consortium (PIDTC) to estimate the clinical impact of granulocyte transfusions on infections or other indications for administration, occurrence of alloimmune/autoimmune complications, and survival outcomes.

Methods

Patients

CGD patients who received granulocyte transfusions pre- (within 6 months) and/or post-HCT or GT were identified from requests to PIDTC and selected non-PIDTC transplant centers. Date of HCT or GT ranged from January 2005 to September 2019. Retrospective deidentified data were collected from the PIDTC database and using a spreadsheet questionnaire filled out by investigators at each participating institution. The study was performed in accordance with site-specific Institutional Review Board–approved protocols as well as the guidelines in the 1964 Declaration of Helsinki and its later amendments.

Clinical Outcomes

Response to granulocyte transfusions in patients with active infection—cleared, partially cleared, stable, or progressive—was determined by the investigator completing the questionnaire based on clinical and radiographic data. Conditioning regimen intensity was classified using CIBMTR workshop definitions [15]. Primary graft failure was defined as lack of neutrophil recovery by day +42 or neutrophil recovery with <10% donor myeloid chimerism. Acute GVHD (aGVHD) was graded based on consensus criteria [16]. Chronic GVHD (cGVHD) was reported as limited or extensive [17].

Statistical Analysis

Binary and categorical variables were summarized by frequency (%), and continuous variables were summarized by median with range. Categorical data were compared using the Chi-squared test. The Mann–Whitney test was used for single comparisons of continuous variables between independent groups. Overall and event-free survival were estimated using the Kaplan–Meier method, and groups were compared using the log-rank test. An event was defined as primary graft failure, receipt of a subsequent transplant, or death.

Results

Granulocyte Transfusions

Twenty-seven patients received granulocyte transfusions pre- and/or post-HCT or GT (Supplemental Table 1). Four patients received granulocyte transfusions in preparation for HCT or GT; 8 patients received granulocyte transfusions both pre- and post-HCT; and 15 patients received granulocyte transfusions during the neutropenic period early post-HCT only. Patients received a median of 11 (range 4–75) granulocyte transfusions. Granulocytes were from related (n = 10, 37%) and unrelated (n = 17, 63%) donors. In no cases were the granulocyte and stem cell donor the same person. The dosing schedule ranged from daily to two times per week. Overall, granulocyte transfusions were well-tolerated. There were 11 (2%) reactions recorded out of a total of 487 transfusions. Reactions included fever and chills (n = 7); fever and chills with hypertension (n = 1); tachypnea with transient oxygen desaturations (n = 1); oxygen desaturations with pulmonary edema on chest X-ray (n = 1); and fever with tachypnea, oxygen desaturations, and hypotension (n = 1). No patient required invasive ventilatory support or vasopressors in the setting of transfusion reactions.

Response to Granulocyte Transfusions Pre-HCT or GT

Twelve patients received granulocyte transfusions prior to HCT or GT. Eleven of the twelve patients received granulocyte transfusions for severe and/or refractory infection, and one patient received granulocyte transfusions for extensive and severe non-infectious inflammatory skin lesions of unclear etiology (Table 1). Patients received a median of 10.5 (range 2–53) granulocyte transfusions pre-cellular therapy, and for the patients who received granulocytes for active infection, the median interval between diagnosis of infection and first granulocyte transfusion was 76 days (range 3–515). Infection cleared or partially cleared in 6 (55%) cases, was stable in 1 (9%) case, and was progressive in 4 (36%) cases at time of HCT or GT. In agreement with a previous report [1], the patients with stable or progressive infection received fewer granulocyte transfusions (median of 6, range 2–10 granulocyte transfusions) than patients whose infections cleared or partially cleared (median of 21.5, range 8–30 granulocyte transfusions, P = 0.015). The patient with
inflammatory skin lesions had no appreciable improvement in the appearance of lesions.

**Response to Granulocyte Transfusions Post-HCT**

Twenty-three patients received granulocyte transfusions during the neutropenic period immediately following allogeneic HCT. Seventeen patients received granulocyte transfusions for active infection at time of transplantation; 5 patients received granulocyte transfusions for infection prophylaxis; and one patient received granulocyte transfusions for pre-existing non-infectious inflammatory skin lesions of unclear etiology (Supplemental Table 1). Eight of the 23 patients had also received granulocyte transfusions prior to HCT as above.

Of the 17 patients with active infection at time of transplantation, 7 patients had received granulocyte transfusions pre-HCT, and 10 patients received granulocyte transfusions post-HCT only. Pre-existing infection failed to clear post-HCT in three cases—all three patients had received granulocyte transfusions pre-HCT and had stable or progressive disease at time of transplantation. Furthermore, one of the
patients had primary graft failure. The remaining 14 patients all had resolution of infection in the setting of donor neutrophil engraftment.

**Alloimmunization**

Two patients received sirolimus with granulocyte transfusions pre-HCT or GT to prevent alloimmunization. None of the patients had baseline anti-HLA antibody testing performed prior to granulocyte transfusions. Ten of the 12 patients who received granulocyte infusions pre-cellular therapy had anti-HLA antibody testing performed, and six of the 10 (60%) patients had anti-HLA antibodies present. One patient had donor-specific antibodies, and two patients had panel-reactive antibodies that included donor HLA mismatches. Patients who developed anti-HLA antibodies received, on average, more granulocyte transfusions pre-HCT or GT compared to patients who did not develop anti-HLA antibodies (21.5 versus 10.8 granulocyte transfusions), although this difference was not statistically significant ($P=0.229$).

In addition, the patient who received GT was found to have anti-platelet antibodies that were attributed to granulocyte transfusions (retrospective testing of this patient’s serum stored from pre-granulocyte transfusions was negative). Two other patients with anti-HLA antibodies were also found to have anti-platelet antibodies in the setting of refractory thrombocytopenia and had positive direct antiglobulin testing within the first 100 days post-HCT. Of note, two patients had received platelet transfusions pre-HCT. Neither of these patients developed anti-HLA or anti-platelet antibodies.

Interestingly, both patients who received sirolimus intended to prevent alloimmunization nonetheless developed anti-HLA or anti-platelet antibodies. Four patients received treatment for anti-HLA antibodies, including rituximab ($n=2$), daratumumab ($n=1$), and a combination plasmapheresis, bortezomib, rituximab, and daratumumab ($n=1$), but anti-HLA antibodies failed to clear in all four cases. Anti-HLA antibodies were not checked for any of the 15 patients who received granulocyte transfusions post-HCT only, but there were no cases of immune-mediated cytopenia within the first 100 days post-HCT.

**HCT and GT Procedures**

Median age at HCT or GT was 12 (range 2–25) years. HCT grafts were from matched related ($n=5$, 20%), matched unrelated ($n=7$, 28%), mismatched related ($n=4$, 16%), and mismatched unrelated ($n=10$, 40%) donors. Stem cell sources were bone marrow (BM) in 3 (12%), umbilical cord blood (UCB) in 9 (36%), and peripheral blood stem cells (PBSC) in 14 (56%) transplants. The patient who underwent gene therapy received lentivirus gene-corrected autologous stem cells as previously described [18]. Details of conditioning regimens and GVHD prophylaxis are shown in Supplemental Table 2. One patient who received granulocyte transfusions pre-HCT died on day 1 from multi-system organ failure and was excluded from HCT and GT outcome analyses.

Patients who received granulocytes pre-HCT or GT (with or without receiving them post-cellular therapy) had lower baseline Lansky or Karnofsky performance scores [median 85 (range 20–100)] than patients who received granulocytes post-HCT only [median 95 (range 70–100), $P=0.013$]. Otherwise, age at HCT or GT, rates of active infection or inflammatory disease, and HCT characteristics were similar between the two groups of patients.

**HCT and GT Outcomes**

HCT and GT outcomes are shown in Table 2. Of the 25 patients who underwent HCT, there were 5 (20%) cases of primary graft failure. All 5 patients received myeloablative conditioning, and stem cell sources were UCB ($n=3$), PBSC ($n=1$), and BM ($n=1$). Three of the patients with primary graft failure received granulocyte transfusions pre-HCT, and all 3 patients had anti-HLA antibodies. Two of the 3 patients had high anti-HLA antibody levels (multiple antibodies with MFI > 10,000 on flow cytometry) but did not have donor-specific antibodies identified (grafts were CD34+ selected PBSC from a 10/10 HLA–matched sibling donor and UCB from a 7/8 HLA–matched unrelated donor). They were both retransplanted, one using the same matched sibling donor with successful engraftment and the other from a different unrelated UCB donor but who died on day +13 prior to donor neutrophil engraftment. The third patient received BM from a 5/10 HLA–matched related donor and was found to have panel reactive antibodies that included donor class I and class II HLA mismatches. The other two patients with primary graft failure received granulocyte transfusions post-HCT only (grafts were from a 6/6 HLA–matched unrelated UCB donor and a 5/6 HLA–matched unrelated UCB donor). Anti-HLA antibodies were not checked for either of the patients. Both patients went on to receive second transplants, again with prophylactic granulocyte transfusions post-HCT, and both patients engrafted successfully. Three of 10 (30%) patients who received granulocyte transfusions pre-HCT had primary graft failure versus 2 of 15 (17%) patients who received granulocyte transfusions post-HCT only. However, this difference was not statistically significant ($P=0.307$). Older age (>18 years), Lansky/Karnofsky performance score <90, active infection or inflammatory disease at time of HCT, and use of HLA–mismatched donors or umbilical cord blood grafts...
| Patient | HCT or GT | Resolution of pre-existing infection | Other infections | Non-infectious complications | Acute GVHD (max grade) | Chronic GVHD | %DHR + neutrophils or myeloid chimerism | Primary graft failure | Secondary graft failure | Outcome |
|---------|-----------|--------------------------------------|------------------|-----------------------------|------------------------|--------------|---------------------------------------|-------------------|----------------------|---------|
| Granulocyte transfusions pre-HCT or GT | | | | | | | | | | |
| 1 | HCT | No | None | None | Engraftment syndrome, ARDS | None | N/A | 99% at day + 20 | N | N/A | Died D + 21 ARDS |
| 2a | GT | No | None | None | ITP, intracranial hemorrhage | N/A | N/A | 44% at 1 month | N | N/A | Died 1 month post-GT from intracranial hemorrhage into pre-existing fungal infection |
| 3 | HCT | N/A | N/A | None | N/A | N/A | N/A | N/A | N/A | N/A | Died on D-1 from MSOF |
| 4 | HCT | Yes | C. difficile colitis | None | None | None | 98% at day + 100 | N | N | Alive and well at 3 years |
| Granulocyte transfusion pre- and post-HCT | | | | | | | | | | |
| 5 | HCT | N/A | CMV viremia | None | Engraftment syndrome | None | N/A | N/A | Y | N/A | Died post-HCT #2 from varicella PNA |
| 6 | HCT | N/A | Adenoviremia; Klebsiella, Bacillus spp. and Fusarium spp.; bacteremia | VOD, AIHA, and ITP | Grade I | N/A | N/A | Y | N/A | Died post-HCT #2 from VOD and MSOF |
| 7 | HCT | Yes | CMV viremia; norovirus gastroenteritis | None | None | None | 100% at day + 100 | N | N | Alive and well at 2 years |
| 8 | HCT | No | CMV viremia; BK viremia; rotavirus gastroenteritis | AIHA, ITP, AKI, pneumonia, and respiratory distress requiring HFNC | Grade III | None | N/A | Y | N | Died at 6 months from diffuse bleeding due to refractory ITP |
| 9 | HCT | No | Adenoviremia and colitis; BK viremia; CMV and EBV PNA | ARDS | Grade III | N/A | 95% at day + 100 | N | N | Died at 3 months from MSOF |
| 10 | HCT | No | CMV pneumonitis; Klebsiella and Aspergillus PNA; Acinetobacter cholangitis and necrotizing liver abscess | Positive lupus anticogulant, diffuse alveolar hemorrhage | Grade IV | N/A | 98% at day + 100 | N | N | Died at 3 months from PNA with diffuse alveolar hemorrhage |
| 11 | HCT | Yes | CMV viremia | None | Grade II | None | 95% at day + 100 | N | N | Alive and well at 3 years |
| 12 | HCT | N/A | Enterococcus bacteremia; C. difficile colitis; MAC, Enterobacter, and HHV-6 PNA | None | Grade II | Limited, mild skin | 100% at day + 100 | N | N | Alive and well at 2 years |
| Granulocyte transfusions post-HCT | | | | | | | | | | |
| 13 | HCT | N/A | None | None | None | N | N/A | N/A | Y | N/A | Alive and well 11 years post-HCT #2 |
| 14 | HCT | N/A | None | None | None | N | N/A | N/A | Y | N/A | Died from heart failure 12 years post-HCT #2 |
| 15 | HCT | Yes | Staphylococcus aureus bacteremia | Pericardial effusion with tamponade, late ITP, MAS, and arthritis | Grade I | N | 100% at day + 100 | N | N | Alive and well at 9 years |
Table 2 (continued)

| Patient | HCT or GT | Resolution of pre-existing infection | Other infections | Non-infectious complications | Acute GVHD (max grade) | Chronic GVHD | %DHR + neutrophils or myeloid chimerism | Primary graft failure | Secondary graft failure | Outcome |
|---------|----------|--------------------------------------|------------------|-------------------------------|------------------------|--------------|------------------------------------------|---------------------|------------------------|---------|
| 16      | HCT      | Yes                                  | CMV viremia, BK hemorrhagic cystitis and viremia | Late ITP, intrahepatic biliary duct dilation, renal atrophy, and urethral stricture | Grade II | Extensive, moderate | 100% at day + 100 | N | N | Alive and well at 9 years |
| 17      | HCT      | N/A                                  | CMV and BK viremia; sinusitis; CONS UTI | Idiopathic PNA syndrome | N | N | 98% at day + 100 | N | N | Alive and well at 6 years |
| 18      | HCT      | N/A                                  | *Citrobacter* and *Klebsiella* bacteremia | Late AIHA and ITP | Grade II | Limited, mild | 100% at day + 100 | N | N | Alive and well at 4 years |
| 19      | HCT      | Yes                                  | Disseminated varicella | None | Grade II | Limited, mild | 100% at day + 100 | N | N | Alive and well at 6 years |
| 20      | HCT      | Yes                                  | Adenoviremia | AKI | Grade II | N | N | N | N | Alive and well at 6 months |
| 21      | HCT      | Yes                                  | None | None | N | N | 99% at day + 100 | N | N | Alive and well at 3 years |
| 22      | HCT      | Yes                                  | None | None | N | N | 100% at day + 100 | N | N | Alive and well at 6 years |
| 23      | HCT      | Yes                                  | None | None | N | N | 96% at day + 100 | N | N | Alive and well at 3 years |
| 24      | HCT      | Yes                                  | *Klebsiella* PNA and bacteremia | None | N | N | 95% at day + 100 | N | N | Alive and well at 3 years |
| 25      | HCT      | Yes                                  | *Enterobacter* perirectal abscess; BK hemorrhagic cystitis and viremia | None | Grade II | N | N | N | N | Alive and well at 3 years |
| 26      | HCT      | Yes                                  | CMV viremia | None | N | N | 98% at day + 100 | N | N | Alive and well at 2 years |
| 27      | HCT      | N/A                                  | EBV viremia | IRIS, late AIHA | N | N | 100% at day + 100 | N | N | Alive and well at 2.5 years |

GVHD graft-versus-host disease, DHR dihydrorhodamine, CMV cytomegalovirus, EBV Epstein-Barr virus, PNA pneumonia, C. difficile Clostridium difficile, MAC mycobacterium avium complex, HHV-6 human herpesvirus 6, CONS UTI coagulase-negative staphylococci urinary tract infection, ARDS acute respiratory distress syndrome, ITP autoimmune thrombocytopenia, AIHA autoimmune hemolytic anemia, VOD veno-occlusive disease, AKI acute kidney injury, HFNC high flow nasal cannula, GT gene therapy, MAS macrophage activation syndrome, IRIS immune reconstitution inflammatory syndrome. MSOF multi-system organ failure. *Gene therapy patient previously reported by Kohn et al.*
were not associated with increased risk of graft failure. There were no cases of secondary graft failure. The patient who received gene therapy had engraftment of gene-corrected autologous stem cells with 44% DHR+ neutrophils at 1 month post-GT.

The estimated 2-year overall survival of the cohort were 73% (95% CI 51–86%), and the 2-year event-free survival was 63% (95% CI 43–78%) (Fig. 1). Overall and event-free survival was both 36% (95% CI 11–63%) in patients who received granulocytes prior to HCT (with or without receiving them following HCT) versus 100% (P < 0.001) and 87% (95% CI 56–97%, P = 0.010) in patients who received them post-HCT only. Similarly, overall and event-free survival were also lower in patients with a baseline Lansky or Karnofsky performance score < 90 [OS and EFS of 25% (95% CI 1–67%) versus 82% (95% CI 58–93%, P = 0.003) and 73% (95% CI 49–87%, P = 0.050), respectively] (Supplemental Fig. 1). Age at HCT, active infection or presence of inflammatory disease at time of HCT, donor and recipient HLA match, conditioning intensity, and stem cell source were not associated with overall or event-free survival (Supplemental Fig. 1).

The three patients with primary graft failure in the setting of alloimmunization all died—one 6 months post-HCT from diffuse bleeding in the setting of refractory immune-mediated thrombocytopenia and two following repeat HCT from varicella pneumonitis and veno-occlusive disease with multi-system organ failure. The patient who underwent GT and developed immune-mediated thrombocytopenia also died 3 months post-therapy due to intracranial hemorrhage. Other causes of death post-HCT included multi-system organ failure (n = 2), pneumonia with diffuse alveolar hemorrhage in a patient with positive lupus anticoagulant (n = 1), and heart failure 11 years post-repeat HCT (n = 1).

Discussion

Granulocyte transfusions were used as adjunctive treatment for severe infection as a bridge to HCT or GT with an overall response rate of 55% in this small cohort. However, their use was associated with a high rate of alloimmunization; 70% of patients developed anti-HLA antibodies or anti-platelet antibodies likely attributable to granulocyte transfusions, and the two patients who received sirolimus with granulocyte transfusions to prevent alloimmunization developed alloantibodies nonetheless. Furthermore, anti-HLA antibodies also appear to be difficult to clear once present, with treatment failing in all 4 cases for which desensitization therapy was attempted. Notably, 3 of 10 (30%) patients who received granulocytes in preparation for HCT had primary graft failure. This is higher than the 12–16% rate of graft failure following HCT reported in recent large cohorts of CGD patients [19–21]. All three patients had anti-HLA antibodies present; however, the role of granulocyte transfusions in graft failure for 2 of the patients is unclear given that donor-specific antibodies were not detected. It is possible given the presence of high levels of anti-HLA antibodies that antibodies to untested HLA and/or minor antigens may have also been present and contributed to primary graft failure. Other patient or transplant-related factors may have also contributed to graft failure; with small patient numbers, it is difficult to draw any conclusions, and, indeed, no statistically significant risk factors for graft failure were identified in this cohort. Importantly, the high rate of primary graft failure in patients who received granulocytes pre-HCT (with or without receiving them post-HCT) as compared to patients who received them post-HCT only was not statistically significant. Again, the small number of patients in this cohort may be hindering our ability to identify an association between the use of granulocyte transfusions pre-HCT and an increased risk of primary graft failure if such a risk exists.
Finally, overall and event-free survival of patients who received granulocyte transfusions pre-HCT or GT was markedly low at 33%. The low survival rates are likely reflective of the overall poor clinical status of these patients as evidenced by their low average baseline performance status rather than the use of granulocytes directly, although bleeding in the setting of severe immune-mediated thrombocytopenia early post-cellular therapy contributed to death in 2 cases. In particular, the patient that underwent GT had successful engraftment of gene-corrected neutrophils before succumbing to an intracranial hemorrhage directly related to immune-mediated thrombocytopenia attributed to granulocyte transfusions. This case demonstrates that granulocyte transfusions may have potential harm even when risk of graft failure and rejection is mitigated as in gene therapy.

Granulocyte transfusions post-HCT were overall well-tolerated and did not appear to be associated with an increased risk of graft failure. Two of 15 (13%) patients who received granulocytes post-HCT only developed graft failure, which is comparable to the reported rate of graft failure following HCT for CGD [19–21]. Both patients were successfully retransplanted, again with prophylactic granulocyte transfusions. Furthermore, there were no cases of early immune-mediated cytopenia in patients who received granulocyte transfusions post-HCT only. However, the efficacy of granulocyte transfusions in this setting is difficult to assess in the setting of concurrent donor neutrophil engraftment and without a comparable control group.

There are a number of limitations to this study, including the small number of patients, the retrospective nature of the survey, and the lack of comparable control groups, making conclusions regarding the efficacy of granulocyte transfusions and associations with transplant outcomes difficult. Furthermore, clinical response to granulocyte transfusions in those with active infection or inflammatory disease was confounded by concomitant antimicrobial and/or anti-inflammatory therapy, and in the post-HCT setting, by donor neutrophil engraftment. There were also inconsistencies in testing for anti-HLA antibodies, not just in terms of whether or not testing was performed but also the specificity of the assay employed (i.e., testing against a panel of antigens versus single antigens to identify donor-specific antibodies).

Ultimately, based on the findings of this survey, we would caution against the use of granulocyte transfusions pre-HCT or GT given the high rates of alloimmunization, primary graft failure, and severe immune-mediated cytopenia post-HCT or GT observed in this small cohort of patients. For patients who do receive granulocyte transfusions pre-HCT or GT, we recommend checking anti-HLA antibodies so that results may be considered during donor selection. Granulocyte transfusions post-HCT do not appear to confer an increased risk of graft failure, although the clinical benefits, if any, of granulocyte transfusions in the post-HCT setting are incompletely understood.

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**Author Contribution** DEA developed the survey, contributed patients, analyzed the data, and wrote the manuscript. DC, SP, RAM, EMK, HLM, and JWL developed the survey, contributed patients, and reviewed the manuscript. KM, JRH, DG, MCL, LMF, ARG, FB, and EA contributed patients and reviewed the manuscript. MJC, CCD, LMG, EH, DBK, LDN, SYP, JMP, MAP, and TT developed the survey and reviewed the manuscript.

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**Data Availability** Not applicable.

**Code Availability** Not applicable.

**Declarations**

**Ethics Approval** The study was performed in accordance with site-specific Institutional Review Board–approved protocols as well as the guidelines in the 1964 Declaration of Helsinki and its later amendments.

**Consent to Participate** Not applicable.

**Consent to Publication** Not applicable.

**Conflict of Interest** MCL is an employee and shareholder of Rocket Pharmaceuticals. FB is a scientific advisor for Eliixirgen Therapeutics. MIC is on the scientific advisory board and has stock ownership for Homology Medicine; on the data and safety monitoring board for Bluebird Bio, Rocket Pharmaceuticals, and Chiesi Pharmaceuticals; and an author for UpToDate. CCD performs consulting with Jazz Pharmaceuticals, Omeros Corporation, and Alexion Inc. JMP receives royalties from UpToDate and her spouse is employed by and holds stock in Invitae Inc. MAP receives honoraria or research funding from Mesoblast and Medexi, Miltenyi Biotec, Equillum Bio, Adaptive Biotechnologies, and Jasper Therapeutics and is on the advisory board of Equillum Bio. TT is a paid consultant for Horizon Pharmaceuticals. DBK is an inventor on intellectual property of the UC Reagents that they have licensed to ImmunoVec on lentiviral vectors and to Lyrik Therapeutics on gene editing. DBK is a member of the Scientific Advisory Boards and/or ad hoc paid consultant to Allogene Therapeutics, Pluto Immunotherapeutics, ImmunoVec, Lyrik Therapeutics, MyoGene Bio, Bluebird Bio, and Sangamo Biosciences. JWL is an employee and shareholder of Bluebird Bio, a consultant and speaker for Horizon Therapeutics, consultant and speaker for Sobi, and on the advisory board for ADMA Biologics. The remaining authors have no
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