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ORIGINAL ARTICLE

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]

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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

Table 1 Response to granulocyte transfusions pre-HCT or GT and development of alloantibodies

Patient	Indication for GTX	Number of GTX	Response	Immune suppression	Anti-HLA antibodies	Other antibodies	Treatment of anti-HLA antibodies	Clearance of anti-HLA antibodies
Granulocyte transfusions pre-HCT or GT								
1	*Burkholderia cepacia* PNA	19	Partially cleared	None	Positive	None	Rituximab + IVIG	No
2[a]	Invasive *Aspergillus fumisynnematous*	6	Progressive	Sirolimus	Negative	Anti-platelet	N/A	N/A
3	Disseminated *Aspergillus nidulans*	8	Partially cleared	Steroids	Not measured	None	N/A	N/A
4	Invasive *Aspergillus viridinutans*	11	Partially cleared	Sirolimus	Positive	None	Rituximab	No
Granulocyte transfusions pre- and post-HCT								
5	Inflammatory skin lesions	53	Stable	None	Positive	None	Daratumumab	No
6	MDR *E. coli* perianal fistulizing disease	30	Cleared	None	Positive	Anti-platelet, DAT positive	Plasmapheresis + bortezomib + rituximab + daratumumab	No
7	Disseminated *Aspergillus fumigatus*	25	Partially cleared	None	Negative	None	N/A	N/A
8	*Geosmithia argillacea* empyema	10	Stable	None	Positive	Anti-platelet, DAT positive	None	No
9	Bacteremia due to multiple pathogens	2	Progressive	None	Negative	None	N/A	N/A
10	*Pyreochaeta romeroi* liver mass	6	Progressive	None	Positive	None	None	No
11	Invasive *Scedosporium apsiospermum* PNA	10	Progressive	None	Negative	None	N/A	N/A
12	*Geosmithia spp.* PNA	24	Cleared	None	Not measured	None	N/A	N/A

GTX granulocyte transfusions, *HLA* histocompatibility locus antigen, *PNA* pneumonia, *MDR* multi-drug resistant, *DAT* direct antiglobulin test, *IVIG* intravenous immunoglobulin. [a]Gene therapy patient previously reported by Kohn et al.[7]

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 pateints 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

Table 2 Transplant and gene therapy outcomes

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	Engraftment syndrome, ARDS	None	N/A	99% at day + 20	N	N/A	Died D + 21 ARDS
2[a]	GT	No	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	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	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 viruria; rotavirus gastroenteritis	AIHA, ITP, AKI, pneumatosis, 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 anticoagulant, 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	N	N/A	N/A	Y	N/A	Alive and well 11 years post-HCT #2
14	HCT	N/A	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 w/ 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	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	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. [a]Gene therapy patient previously reported by Kohn et al.[7]

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.

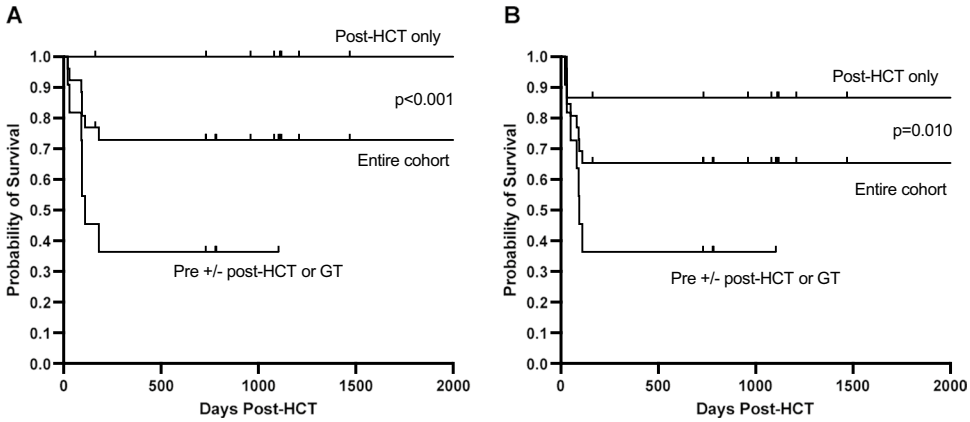

Fig. 1 **A** Overall and **B** event-free survival post-HCT or GT. P-values are comparing survival curves of patients who received granulocyte transfusions pre- ± post-HCT or GT to patients who received granulocyte transfusions post-HCT or GT only

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 poteintial 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 re-transplanted, 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.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10875-022-01261-1.

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 for Publication Not applicable.

Conflict of Interest MCL is an employee and shareholder of Rocket Pharmaceuticals. FB is a scientific advisor for Elixirgen Therapeutics. MJC 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 Pharmaceutical; and an author for UpToDate. CCD perfoms 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, Equillium Bio, Adaptive Biotechnologies, and Jasper Therapeutics and is on the advisory board of Equillium 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 spearker 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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