HHS Public Access

Author manuscript

Lancet Haematol. Author manuscript; available in PMC 2023 September 01.

Published in final edited form as:

Lancet Haematol. 2022 September ; 9(9): e660–e669. doi:10.1016/S2352-3026(22)00206-X.

Haploidentical bone marrow transplantation in patients with relapsed or refractory severe aplastic anaemia in the USA (BMT CTN 1502): a multicentre, single-arm, phase 2 trial

Amy E DeZern,
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA

Mary Eapen,
Division of Hematologic Malignancies, Medical College of Wisconsin, Milwaukee, WI, USA

Juan Wu,
The EMMES Company, Rockville, MD, USA

Julie-An Talano,
Division of Hematologic Malignancies, Medical College of Wisconsin, Milwaukee, WI, USA

Melhem Solh,
The Blood and Marrow Transplant Program at Northside Hospital, Atlanta, GA, USA

Blachy J Dávila Saldaña,
Children's National Health System, Washington, DC, USA

Chatchada Karanes,
City of Hope National Medical Center, Duarte, CA, USA

Mitchell E Horwitz,
Duke University School of Medicine, Durham, NC, USA

Kanwaldeep Mallhi,
Fred Hutchinson Cancer Research Center, Seattle, WA, USA

Sally Arai,

Correspondence to: Dr Amy E DeZern, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD 21287, USA adezern1@jhmi.edu .

Contributors

AED, MAP, and ME designed the study, treated the patients, accessed and verified the data, analysed the results, and wrote the manuscript. JW and BRL performed the statistical analysis and wrote the manuscript. J-AT, MS, BJDS, CK, MEH, KM, SA, NF, EH, PW, JHA, HJD, EL, RAB, BRL, MMH, and RJJ advised on the protocol, treated the patients (at centres where patients were enrolled), analysed the results, and reviewed the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Deidentified participant data for BMT CTN 1502 will be deposited in the National Heart, Lung, and Blood Institute Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC), a publicly available database. Study documents, including the study protocol, informed consent form, data dictionary, and case report forms for data collection are also available via the repository. Data will become accessible 3 years after the end of clinical activity and 2 years after the primary publication, as anticipated in 2024. Instructions on specimen or data requests and contact information for BioLINCC are also available.

Blood and Marrow Transplantation and Cellular Therapy Division, Stanford University, Stanford, CA, USA

Nosha Farhadfar,
UF Health Bone Marrow Transplant, University of Florida, Gainesville, FL, USA

Elizabeth Hexner,
University of Pennsylvania School of Medicine, Philadelphia, PA, USA

Peter Westervelt,
Washington University School of Medicine, St Louis, MO, USA

Joseph H Antin,
Dana-Farber Cancer Institute, Boston, MA, USA

H Joachim Deeg,
Fred Hutchinson Cancer Research Center, Seattle, WA, USA

Eric Leifer,
Intramural Research, National Heart, Lung, and Blood Institute, Bethesda, MD, USA

Robert A Brodsky,
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA

Brent R Logan,
Division of Hematologic Malignancies, Medical College of Wisconsin, Milwaukee, WI, USA

Mary M Horowitz,
Division of Hematologic Malignancies, Medical College of Wisconsin, Milwaukee, WI, USA

Richard J Jones,
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA

Michael A Pulsipher
Huntsman Cancer Institute, Salt Lake City, UT, USA

Summary

Background—Relapsed severe aplastic anaemia is a marrow failure disorder with high morbidity and mortality. It is often treated with bone marrow transplantation at relapse post-immunosuppressive therapy, but under-represented minorities often cannot find a suitably matched donor. This study aimed to understand the 1-year overall survival in patients with relapsed or refractory severe aplastic anaemia after haploidentical bone marrow transplantation.

Methods—We report the outcomes of BMT CTN 1502, a single-arm, phase 2 clinical trial done at academic bone marrow transplantation centres in the USA. Included patients were children and adults (75 years or younger) with severe aplastic anaemia that was refractory (fulfilment of severe aplastic anaemia disease criteria at least 3 months after initial immunosuppressive therapy) or relapsed (initial improvement of cytopenias after first-line immunosuppressive therapy but then a later return to fulfilment of severe aplastic anaemia disease criteria), adequate performance status (Eastern Cooperative Oncology Group score 0 or 1, Karnofsky or Lansky score ≥60%), and the presence of an eligible related haploidentical donor. The regimen used reduced-intensity

conditioning (rabbit anti-thymocyte globulin 4·5 mg/kg in total, cyclophosphamide 14·5 mg/kg daily for 2 days, fludarabine 30 mg/m^2 daily for 5 days, total body irradiation 200 cGy in a single fraction), related HLA-haploidentical donors, and post-transplantation cyclophosphamide-based graft-versus-host disease (GVHD) prophylaxis. Additionally, for GVHD prophylaxis, mycophenolate mofetil was given orally at a dose of 15 mg/kg three times a day up to 1 g three times a day (maximum dose 3000 mg per day) from day 5 to day 35, and tacrolimus was given orally or intravenously from day 5 to day 180 as per institutional standards to maintain a serum concentration of 10–15 ng/mL. The primary endpoint was overall survival 1 year after bone marrow transplantation. All patients treated per protocol were analysed. This study is complete and is registered with ClinicalTrials.gov, NCT02918292.

Findings—Between May 1, 2017, and Aug 30, 2020, 32 patients with relapsed or refractory severe aplastic anaemia were enrolled from 14 centres, and 31 underwent bone marrow transplantation. The median age was 24·9 years (IQR 10·4–51·3), and median follow-up was 24·3 months (IQR 12·1–29·2). Of the 31 patients who received a transplant, 19 (61%) were male and 12 (39%) female. 13 (42%) patients were site-reported as non-White, and 19 (61%) were from under-represented racial and ethnic groups; there were four (13%) patients who were Asian, seven (23%) Black, one (3%) Hawaiian/Pacific Islander, and one (3%) more than one race, with seven (23%) patients reporting Hispanic ethnicity. 24 (77%) of 31 patients were alive with engraftment at 1 year, and one (3%) patient alive with autologous recovery. The 1-year overall survival was 81% (95% CI 62–91). The most common grade 3–5 adverse events (seen in seven or more patients) included seven (23%) patients with abnormal liver tests, 15 (48%) patients with cardiovascular changes (including sinus tachycardia, heart failure, pericarditis), ten (32%) patients with gastrointestinal issues, seven (23%) patients with nutritional disorders, and eight (26%) patients with respiratory disorders. Six (19%) deaths, due to disease and unsuccessful bone marrow transplantation, were reported after transplantation.

Interpretation—Haploidentical bone marrow transplantation using this approach results in excellent overall survival with minimal GVHD in patients who have not responded to immunosuppressive therapy, and can expand access to bone marrow transplantation across all populations. In clinical practice, this could now be considered a standard approach for salvage treatment of severe aplastic anaemia. Attention to obtaining high cell doses (>2·5 × 10^8 nucleated marrow cells per kg of recipient ideal bodyweight) from bone marrow harvests is crucial to the success of this approach.

Introduction

Severe aplastic anaemia is an immune-mediated, acquired haematopoietic stem-cell disorder that presents with hypocellular marrow and pancytopenia.[1] Severe aplastic anaemia is associated with early and late morbidity and mortality. Infection, often fungal, in the setting of severe neutropenia is the most common cause of early death; however, haemorrhage, myelodysplastic syndrome, acute myeloid leukaemia, paroxysmal nocturnal haemoglobinuria, avascular necrosis, and transfusional iron overload are other causes of severe morbidity and mortality.[2] Improved supportive care has led to substantial progress in controlling the acute aspects of the disease. Nevertheless, late complications of severe aplastic anaemia after immunosuppressive therapy, especially the risk of

relapse and secondary clonal neoplasms, remain a substantial concern. The anticipated haematopoietic response rate to first-line immunosuppressive therapy is about 70–80%, and the probability of overall survival at 5 years ranges from 60% to 85%.[3] However, failure-free survival (survival without relapse or secondary clonal disease beyond 10 years) after immunosuppressive therapy is less than 50%.[4] Confirming the safety of a haploidentical platform in this setting is crucial to broaden therapeutic options at relapse. Data emphasise limitations to long-term clinical success and the shortcomings of immunosuppressive therapy,[5–7] and additional therapeutic options are warranted for these patients.

Allogeneic bone marrow transplantation in severe aplastic anaemia can rapidly reconstitute haematopoiesis and decrease the risk of relapse and secondary clonal disease. Allogeneic bone marrow transplantation produces long-term survival approaching 90% at 5 years in patients younger than 20 years, and more than 75% for patients older than 20 years. Older patients, especially those older than 40 years, historically have less favourable transplantation outcomes, attributable to issues including higher rates of graft failure and graft-versus-host disease (GVHD). Additionally, identifying fully matched donors is particularly difficult for some ethnic groups, such as patients of African descent and Hispanic patients, reflecting high HLA diversity and under-representation in donor registries.[8] Allogeneic bone marrow transplantation using alternative donors, including related HLA-haploidentical donors, has been relegated to late in the therapeutic algorithm,[9,10] owing to concerns of transplantation-related morbidity and mortality.[11,12]

Post-transplantation cyclophosphamide has greatly improved the safety and efficacy of alternative donor bone marrow transplantation by facilitating engraftment and decreasing the risk of GVHD, even with high degrees of HLA mismatch.[13–15] Overall outcomes following haploidentical bone marrow transplantation with post-transplantation cyclophosphamide in haematological malignancies are similar to outcomes with matched unrelated donors.[16] Furthermore, with the use of rabbit anti-thymocyte globulin during conditioning and tacrolimus for 6 months to a full year to further reduce the risk of GVHD, this platform is effective in non-malignant diseases,[9,10,17–19] in which a graft-versus-tumour effect is not necessary. The approach in relapsed or refractory severe aplastic anaemia using haploidentical donors led to good overall survival in a singleinstitution study,[20] but required validation in a multicentre prospective trial. Thus, we present the results of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 1502, a prospective clinical trial of haploidentical donor allogeneic bone marrow transplantation with post-transplantation cyclophosphamide for relapsed or refractory severe aplastic anaemia.

Methods

Study design and participants

BMT CTN 1502 was a single-arm, phase 2 clinical trial done at academic bone marrow transplantation centres in the USA. Included patients were 75 years or younger with a diagnosis of acquired severe aplastic anaemia who had not responded to at least one course of immunosuppressive therapy without a fully matched related sibling donor available, but with a haploidentical marrow donor available. Absence of response to immunosuppressive therapy was defined in the protocol as refractory (persistence of severe cytopenias and

fulfilment of severe aplastic anaemia disease criteria at least 3 months after initial immunosuppressive therapy) or having relapsed (initial improvement of cytopenias after first-line immunosuppressive therapy but then a later return to fulfilment of severe aplastic anaemia disease criteria when immunosuppressive therapy was decreased or ceased). The choice of immunosuppressive therapy and number of courses of immunosuppressive therapy before bone marrow transplantation were at the discretion of the treating physician. Data on previous therapies were not collected in detail on this protocol. Patients needed adequate organ function as previously reported.[15] Additional eligibility criteria included adequate performance status (Eastern Cooperative Oncology Group score 0 or 1, Karnofsky or Lansky score ≥60%), ability to provide written informed consent (and assent as appropriate for minors), and the presence of an eligible related haploidentical donor. Monosomy 7 was specifically excluded as it is considered to be consistent with myelodysplastic syndrome or leukaemia. Exclusion criteria included inherited bone marrow failure syndrome, previous haematopoietic stem-cell or solid organ transplantation, uncontrolled infection, and inadequate organ function.

The study protocol was approved by institutional review boards at all participating sites. The study was initially designed to enroll patients to an unrelated cord blood group in addition to the haploidentical group. Due to lack of accrual to the unrelated cord blood group, this group was closed 8 months after the study opened at the recommendation of the data safety monitoring board. The unrelated cord blood group was removed from the protocol for version 2.0, which was released on June 19, 2018. An independent medical monitor and the data safety monitoring board oversaw trial safety and integrity with patients monitored for graft failure and death.

Procedures

A suitable donor was defined as an available haploidentical relative of the patient, including biological parents, siblings or half siblings, children, uncles or aunts, first cousins, and extended relatives. Eligible haploidentical donors had two to four mismatches if HLA-A, HLA-B, HLA-C, and HLA-DRB1 typing was used; two to five mismatches if HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1 typing was used; and two to six mismatches if HLA-A, HLA-B, HLA-C, HLA-DRB1, HLA-DQB1, and HLA-DPB1 typing was used. A unidirectional mismatch in either the graft-versus-host or host-versus-graft direction was considered a mismatch. The donor was defined as a full haplotype match by being identical at a minimum of one allele (at high-resolution DNA-based typing) at the following genetic loci: HLA-A, HLA-B, HLA-C, and HLA-DRB1 if eight-allele typing was used; HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1 if ten-allele typing was used; and HLA-A, HLA-B, HLA-C, HLA-DRB1, HLA-DQB1, and HLA-DPB1 if 12-allele typing was used by the local centre. Donor-specific antibodies (at mean fluorescence intensity >1000 by solid phase immunoassay) were an exclusion criterion.

Donor bone marrow was harvested with a target yield of 4×10^8 nucleated marrow cells per kg of recipient ideal bodyweight[21] and infused on day 0. Dose of nucleated marrow cells per kg was calculated as previously described.[21] The marrow was unmanipulated except that major ABO-incompatible grafts were red blood cell depleted by buffy coat preparation

and minor ABO-incompatible grafts were plasma depleted as per institutional standards. Correlatives included telomere length before bone marrow transplantation in all consenting patients and consenting donors.

Rabbit anti-thymocyte globulin (Thymoglobulin [Sanofi]) was dosed at 0·5 mg/kg on day −9 and at 2 mg/kg on days −8 and −7, intravenously. Fludarabine was administered at 30 mg/m^2 intravenously daily for 5 days, from day −6 to day −2 (total dose received 150 mg/m^2). Cyclophosphamide was given at 14·5 mg/kg intravenously daily for 2 days from day −6 to day −5 and administered as a 1–2 h infusion (total dose received 29 mg/kg) and total body irradiation was delivered in a single fraction of 200 cGy on day −1. The marrow graft was infused on day 0. Filgrastim was given on day 5 at 5 μg/kg per day and continued until absolute neutrophil count was greater than 1·5 × 10^9 cells per L for 3 days. In addition to rabbit anti-thymocyte globulin, GVHD prophylaxis included post-transplantation cyclophosphamide administered at 50 mg/kg per day intravenously on days 3 and 4; mycophenolate mofetil given at a dose of 15 mg/kg orally three times a day up to 1 g three times a day (maximum dose 3000 mg per day) from day 5 to day 35; and tacrolimus given orally or intravenously from day 5 to day 180 as per institutional standards to maintain a serum concentration of 10–15 ng/mL.

Blood product replacement and other supportive care measures were per institutional practices, as were prophylactic and empirical antibiotics, antifungal prophylaxis, *Pneumocystis jirovecii* pneumonia prophylaxis, and intravenous immunoglobulin. Patients were monitored for viral reactivation by weekly measurement of cytomegalovirus and Epstein-Barr virus copy number by PCR of serum until day 100. If a patient had evidence of viral reactivation, it was managed at the discretion of the treating site. Human herpesvirus 6 copy number was monitored weekly until day 60. In the event of development of either acute or chronic GVHD, therapy was at the discretion of treating centres. The same was true for the management of graft failure.

Adverse event reporting was consistent with the BMT CTN manual of procedures.[22] Adverse events were assessed at multiple timepoints (day 28, day 56, day 100, day 180, and day 365) after transplantation using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Of note, the study did not collect data on grade 1–2 toxicities as per the BMT CTN manual of procedures (although grade 2 infection data were collected). Donor chimerism studies were done on peripheral blood or bone marrow on days 28, 56, 180, and 360. Lineage-specific, myeloid, and T-cell chimerism were required. The management beyond any documented graft failure was not specified by this protocol. Acute GVHD was graded by consensus grading as per the BMT CTN manual of procedures. Assessment for acute GVHD was done weekly up to day 100 and then monthly to 1-year post-transplantation. The time of onset of grades 2–4 and grades 3–4 acute GVHD were recorded, as well as the maximum grade incurred. Chronic GVHD was assessed on the basis of 2014 US National Institutes of Health Consensus Criteria.[23] Quantitative assessments of peripheral blood CD3, CD4, CD8, and CD56-positive lymphocytes were measured by flow cytometric analysis at baseline, day 100, day 180, and day 365 post-transplantation to monitor for immune reconstitution. Health-related quality of life was measured at baseline and then change from baseline at day 100, day 180, and day 365 post-transplantation using

two instruments: the Medical Outcomes Study 36-Item Short Form Healthy Survey (SF-36) for adult participants (older than 18 years), and the PedsQLTM Stem Cell Transplant Module for paediatric participants (8–18 years).

Outcomes

The primary endpoint was overall survival 1 year after bone marrow transplantation. For overall survival, death from any cause was considered an event and surviving patients were censored at last follow-up. The secondary endpoints were assessment of the proportion of patients alive and engrafted, neutrophil and platelet recovery, graft failure (primary and secondary), grade 2–4 acute GVHD and chronic GVHD, immune reconstitution, infectious complications (cytomegalovirus viraemia and disease, Epstein-Barr virus viraemia with or without post-transplantation lymphoproliferative disorder), and health-related quality of life, all within the first year after transplantation.

Alive with engraftment was described using graft-failure-free survival, with events including death, primary graft failure, and secondary graft failure; patients alive without graft failure were censored at last follow-up. Neutrophil recovery was defined as an absolute neutrophil count of more than $0{\cdot}5 \times 10^9$ cells per L on three consecutive measurements on different days. Platelet recovery was defined as a platelet count greater than 20×10^9 platelets per L for 7 days without transfusion. Primary graft failure was defined by the lack of neutrophil engraftment by day 56 following bone marrow transplantation or not having at least 5% donor chimerism (whole blood or marrow) on any measurement up to and including day 56. Patients could have met this definition before day 56. Secondary graft failure was defined as any one of the following: initial neutrophil engraftment followed by sustained subsequent decline in absolute neutrophil count to less than $0{\cdot}5 \times 10^9$ cells per L for three consecutive measurements on different days; or initial whole blood or marrow donor chimerism greater than or equal to 5%, but then declining to less than 5% on subsequent measurements; or second infusion or transplantation given for graft failure.

In an additional prespecified exploratory analysis, recipient and donor telomere length was assessed by flow cytometry fluorescent in-situ hybridisation (FISH) in lymphocytes and granulocytes in the standard clinical fashion.[24] These results were then analysed with clinical outcomes. Patients and donors could choose to consent to this testing separately.

Statistical analysis

The primary hypothesis was that haploidentical bone marrow transplantation for severe aplastic anaemia using the protocol regimen would result in overall survival at 1 year after bone marrow transplantation of 75% or greater. The sample size of 30 patients was calculated so that an observed overall survival of 75% would have a 95% Wald confidence interval with a margin of error of plus or minus 15·5% on the basis of a binomial proportion assuming complete 1-year followup of study participants. The lower bound of this confidence interval would exclude a true overall survival rate of 59%, which is close to historical overall survival rates with haploidentical transplantations reported to the Center for International Blood and Marrow Transplant Research. Overall survival and graft-failure-free survival were described using the Kaplan-Meier estimator. Cumulative

incidences of GVHD, neutrophil recovery, platelet recovery, toxicity, and infection events were summarised using the Aalen-Johansen estimator along with 95% confidence intervals; death was considered as a competing risk. Confidence interval estimates for the cumulative incidence function at a fixed timepoint were constructed using a point estimate and its variance estimate obtained from the Aalen-Johansen estimator of cumulative incidence. The SF-36 physical and mental component scores for adult patients and the PedsQL Stem Cell Transplant Module for paediatric patients are summarised for each timepoint, as well as change from baseline to each timepoint after transplantation, compared by the paired *t*-test. Other endpoints were summarised using descriptive statistics. Analyses were performed using SAS version 9.4 and R version 3.6. This study is registered with ClinicalTrials.gov, NCT02918292.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between May 19, 2017, and Aug 31, 2020, 32 patients were enrolled from 14 centres (figure 1). 31 of 32 patients enrolled received a transplant. One 65-year-old White Hispanic male patient died of bacterial infection after enrolment but before receiving any protocol treatment. The majority of patients underwent transplantation well after initial diagnosis; however, five patients underwent transplantation within 6 months of diagnosis, allowable on protocol, because their cytopenia was deemed too severe to wait additional months to respond to previous immunosuppressive therapy. All other data describe the 31 patients who received a transplant. Of the 31 transplant recipients, 19 (61%) were male, with 13 (42%) of the cohort site-reported as non-White (table 1). There were four (13%) patients who were Asian, seven (23%) Black, one (3%) Hawaiian/Pacific Islander, and one (3%) more than one race, with seven (23%) patients reporting Hispanic ethnicity. The median age at enrolment was 24·9 years (IQR 10·4–51·3). No patients had donor-specific HLA antibodies requiring desensitisation against their donors as specified in the protocol. The median age of haploidentical donors was 38·6 years (26·9–46·5).

1-year overall survival was 81% (95% CI 62–91; appendix p 7). The median follow-up for all patients was 24–3 months (IQR 12–1-29–2). 24 (77%) of 31 patients were alive with sustained engraftment at 1 year. Seven (23%) patients did not meet this endpoint, including four (13%) patients with primary graft failure, one (3%) patient with secondary graft failure, and two (6%) deaths without graft failure. There were no withdrawals reported on the study.

Six (19%) deaths were reported after transplantation. The site-reported primary causes of death include graft failure (n=1), fungal infection (n=1), organ failure (n=2), interstitial pneumonia (n=1), and encephalopathy (n=1). Two of these deaths occurred due to complications after the first transplantation procedure. Overall, five patients (16%) developed graft failure and all went on to receive a second transplant. Four of these five patients died due to complications of their second transplantation procedure (three had

developed primary graft failure and one secondary graft failure). Additional adverse events are noted, by grade, in table 2.

Donor bone marrow was harvested with a target yield of 4×10^8 nucleated marrow cells per kg of recipient ideal bodyweight,[21] and a recommended minimum yield of $2{\cdot}5 \times 10^8$ nucleated marrow cells per kg of recipient ideal bodyweight. The marrow grafts had a median total nucleated marrow cell count of $4{\cdot}4 \times 10^8$ cells per kg of recipient ideal bodyweight (IQR $3{\cdot}0–5{\cdot}5 \times 10^8$), a median $CD34^+$ cell count of $3{\cdot}9 \times 10^6$ cells per kg of recipient ideal bodyweight ($2{\cdot}5–6{\cdot}5 \times 10^6$) and a median $CD3^+$ cell count of $14{\cdot}6 \times 10^7$ cells per kg of recipient ideal bodyweight ($6{\cdot}7–31{\cdot}8 \times 10^7$). Among the 31 patients who received a transplant, four (13%) did not attain the minimum marrow cell counts according to the guidelines for minimum donor harvest included in the protocol, attaining cell counts of $1{\cdot}7 \times 10^8$, $1{\cdot}9 \times 10^8$, $2{\cdot}0 \times 10^8$, and $2{\cdot}0 \times 10^8$ nucleated marrow cells per kg of recipient ideal body-weight. Three of these four patients developed either primary graft failure or secondary graft failure. The fourth patient attained long-term engraftment. This finding illustrates the decreased graft-failure-free survival in patients with low-cell-dose allografts, as these patients had only 50% (95% CI 6–85) 1-year overall survival, mostly due to a 25% (1–67) 1-year graft-failure-free survival rate. In contrast, patients receiving more than $2{\cdot}5 \times 10^8$ nucleated marrow cells per kg of recipient ideal bodyweight had a 1-year graft-failure-free survival rate of 85% (65–94).

The proportion of patients alive and engrafted at 1 year (graft-failure-free survival) was 77% (95% CI 58–89; 24 of 31 patients). 22 patients had sustained 100% donor chimerism in both myeloid and T-cell compartments at 1 year, and two patients had mixed chimerism with more than 95% donor chimerism in both myeloid and T-cell compartments at 1 year. One patient was alive at 1 year but with only 4% donor chimerism in the myeloid lineage, indicative of autologous recovery with improved blood counts.

29 (94%) of 31 patients had neutrophil recovery by day 28. The median time to neutrophil recovery was 17 days (IQR 15–19). The day-28 cumulative incidence of neutrophil recovery was 94% (95% CI 72–99). The median time to engraftment as defined by ANC recovery (for the 27 patients who did not develop primary graft failure) was 17 days (IQR 15–19). Among the 24 patients who had platelet recovery by day 100, the median time of platelet recovery to 20 000 platelets per μL or greater was 23 days (IQR 17–33; appendix p 6). The day-100 incidence of platelet recovery was 77% (95% CI 57–89).

19 (61%) of 31 patients developed infections after transplantation (appendix p 3). Of these 19 patients, 12 developed a maximum of grade 2 infection and seven a maximum of grade 3 infection. Grade 2 or higher infection occurred in five (100%) of five patients with graft failure and 14 (54%) of 26 patients without graft failure. Four of the documented grade 3 infections (three fungal and one bacterial) occurred in the five patients with graft failure. The majority of all documented infections were bacterial, followed by viral. Three patients had documented fungal infections and all were in patients with graft failure.

Seven (23%) of 31 patients developed cytomegalovirus reactivation, three (10%) had Epstein-Barr viraemia detected in routine testing, and two (6%) were diagnosed with post-

transplantation lymphoproliferative disorder with positive viraemia. All of these infections were successfully treated (ie, the patients had undetectable viral loads). The 1-year cumulative incidence, treating death as a competing risk, was 23% (95% CI 10–39) for cytomegalovirus infection, 10% (2–23) for Epstein-Barr virus infection, and 7% (1–19) for post-transplantation lymphoproliferative disorder.

The day-100 cumulative incidence of grade 2–4 acute GVHD was 16% (95% CI 6–31); all five of the cases were grade 2. Eight (26%) of 31 patients developed chronic GVHD. One case was moderate and the others were mild chronic GVHD; three of these eight patients were not on immunosuppressive therapy at 1 year (appendix p 2). The 1-year incidence of chronic GVHD was 26% (12–42; figure 2). All patients with chronic GVHD and at least 2 years of follow-up were reported to be off therapy. The GVHD-free survival (an exploratory composite endpoint of survival without grade 3–4 acute GVHD or any chronic GVHD) was 55% (36–70).

Quantitative assessments of peripheral blood CD3, CD4, CD8, and CD56-positive lymphocytes showed that, notably, T-cell counts (CD3, CD4, and CD8) decreased substantially after bone marrow transplantation and slowly returned to baseline counts by 1 year. As expected, natural killer cells and B cells were very low before transplantation, with natural killer cells rising quickly after transplantation and reaching a plateau by 6 months, while B cells recovered slowly over the first year (appendix p 8).

21 (68%) of 31 patients were alive and evaluable for health-related quality of life surveys at 1 year; 15 (nine adults and six children; 71% completeness among survivors) had completed both baseline and 1-year surveys (appendix p 4). For the six evaluable children, there was significant improvement in their physical, emotional, social, and school functions from before transplantation to 1 year after transplantation. Similarly, for the nine evaluable adults, there was significant improvement in their physical component scores (general health, pain, physical, emotional, and social functions) from before transplantation to 1 year after transplantation. Participants did not report significant changes in mental component scores between baseline and other timepoints studied.

For this cohort of patients with known acquired severe aplastic anaemia, normalised delta telomere lengths were in the normal range (>1st–99th percentile) for all donors and nearly all patients. Two patients had borderline low values in the granulocytes (with neutropenia) but not in the lymphocytes. No significant associations were observed between the age-adjusted telomere length and clinical outcomes of survival or engraftment (data not shown).

Discussion

Here we show, in a multicentre study, overall survival of 81% and graft-failure-free survival of 77% with haploidentical bone marrow transplantation in heavily pretreated paediatric and adult patients with relapsed or refractory severe aplastic anaemia without an HLA-matched sibling or HLA-matched unrelated donor. These findings have great clinical relevance, given that the prognosis for patients with severe aplastic anaemia treated with immunosuppressive therapy remains suboptimal, with response rates of less than 80%,

relapse rates up to 40%, and evolution to myelodysplastic syndrome in more than 15% of patients in their lifetime.[5,25] For the more than 40% of patients with disease that is refractory to immunosuppressive therapy, the risk of death from bleeding or infection within 5 years has historically been more than 50% in patients ineligible for bone marrow transplantation.[26] Six patients older than 60 years were enrolled on this study and all engrafted, with only one death in this age group. Additionally, this trial was able to enroll 61% of patients who self-identified their race and ethnicity as non-Hispanic White.

Long-term failure-free survival for patients treated with immunosuppressive therapy is poor. The median follow-up for nearly 200 patients treated on a prospective trial of equine anti-thymocyte globulin with ciclosporin (with or without trial growth factor support) was 11·7 years and showed an overall survival at 15 years of 60%. Event-free survival was only 23%, with events including relapse, transplantation, secondary myelodysplastic syndrome or acute myeloid leukaemia, and death.[7] At the time of relapse for a patient with severe aplastic anaemia, eltrombopag is currently the only therapy for salvage approved by the US Food and Drug Administration. There is a published response rate of 44% for a single lineage response, but less than 25% of patients achieved a trilineage response.[27] Concern has been raised about insufficient durability and longterm complications. Data suggest that the addition of eltrombopag upfront improved rapidity and rates of response over anti-thymocyte globulin and ciclosporin among previously untreated patients.[6] With follow-up, relapse occurred at shorter median times with the three-drug combination,[5,6] further demonstrating a need for alternative approaches for these patients after immunosuppressive therapy. Although salvage with repeat immunosuppressive therapy has been attempted in some patients, intensification of the regimen with more potent drugs, such as rabbit anti-thymocyte globulin, sirolimus, alemtuzumab, or mycophenolate, has not improved response rates, which are generally 40% or less. This is a patient group in need of effective therapies at relapse or non-responsiveness after immunosuppressive therapy, as highlighted as an area of medical need for patients with severe aplastic anaemia by the 2014 BMT CTN Scientific Symposium. The approach presented here originated in a single-centre trial,[15,20] the results of which were validated in this multicentre trial. The survival shown in the single-centre trial (overall survival 94% [90% CI 88–100]) and the multicentre results reported here (overall survival 81% [95% CI 62–91]) have overlapping CIs, which is reassuring for the broader applicability of this platform in severe aplastic anaemia.[15] Limitations of the current study include a paucity of available information on the previous immunosuppressive therapies (number of cycles, response, and duration of response) before enrolment, relatively low numbers of patients despite the study's multicentre nature, and limited characterisation of the bone marrow graft. Additionally, we followed up patients for cytomegalovirus and Epstein-Barr virus reactivation but not for human herpesvirus 6 reactivation in the long term.

Availability of HLA-matched donors has been a limitation to bone marrow transplantation at relapse in severe aplastic anaemia. Although results of bone marrow transplantation from alternative donors for malignant diseases are improving,[15] particularly with the use of post-transplantation cyclophosphamide, there has been reluctance to adopt this approach for severe aplastic anaemia. The results of this study support the idea that this curative path for severe aplastic anaemia can be offered to all patients, including under-represented

minorities, who historically have a low likelihood of finding a matched donor. More than 60% of patients on this trial were from groups other than non-Hispanic White.

The necessity of adequate cell dose to facilitate engraftment and survival is very evident in this small dataset. Additionally, severe infections and toxicities occurred more frequently in patients who had early or late graft rejection than in those who had no graft rejection; thus, high cell dose to maximise engraftment is a key to optimal outcomes, as seen in a similar Brazilian series.[28] Bone marrow harvesting is now performed less commonly than in past decades, with more widespread use of peripheral blood grafts, and experience is lacking. 1 year after trial initiation, a series of rejections were reported in patients receiving very small numbers of cells, and three of the first nine patients received grafts with small numbers of cells. Training was provided to all sites on optimal harvest procedures. This training resulted in larger harvested cell doses, and only one of 22 subsequent patients received a small cell dose.

Patients, their families, and sometimes their providers often have concerns about the long-term toxicities of bone marrow transplantation in severe aplastic anaemia. Data here should be reassuring. Chronic GVHD was low in both incidence and severity. Health-related quality of life increased to normal levels in patients who engrafted, especially in adults, indicating the tolerance of this platform and the benefit of improved haematopoiesis with engraftment. It is acknowledged that long-term follow-up of patients receiving the post-transplantation cyclophosphamide regimen must continue and assessment of late effects is ongoing, in patients transplanted for both malignant and non-malignant diseases. We believe these data support the use of a minimum of 200 cGy in a single fraction of total body irradiation for patients with relapsed severe aplastic anaemia. However, other series have shown a benefit of augmentation to the dose of total body irradiation to further facilitate engraftment in highly sensitised patients and treatment-naive patients.[15,28]

Conflicting reports[29] on the effect of telomere length on survival outcomes for patients with severe aplastic anaemia has confounded our understanding of how to use this testing clinically. Most studies have used PCR-based methods as opposed to the Clinical Laboratory Improvement Amendments-certified flow cytometry-FISH that was applied here. The analysis in this trial does not support any difference in outcomes, by telomere length, with this platform. However, the number of patients studied was small and the power to detect an effect might be limited.

This study provides evidence for the role of haplo-identical bone marrow transplantation using a post-transplantation cyclophosphamide-based regimen and a bone marrow graft for patients with severe aplastic anaemia after failure of immunosuppressive therapy or relapse after immunosuppressive therapy. Furthermore, it shows the importance of adequate graft cell dose with minimum requirement of $2{\cdot}5 \times 10^8$ marrow mononuclear cells to optimise engraftment. We suggest that haematopoietic stem-cell transplantation should be pursued at 3–6 months after immunosuppressive therapy if the patient still meets criteria for severe disease or as the immediate option at the time of relapse, forgoing further toxicity such as readdition of ciclosporin, eltrombopag, or other toxic immunosuppressive therapy platforms.[30] Although 200 cGy was sufficient for engraftment here in the majority of

patients, 400 cGy appeared to result in better engraftment, without increased toxicity, in other series and in the treatment-naive setting.[15] The success of this approach in the salvage setting should encourage further study to evaluate its efficacy earlier in the disease course for patients with severe aplastic anaemia, as was recommended by the most recent BMT CTN State of the Science Symposium.[31] Validation of upfront transplantation for patients with severe aplastic anaemia in multicentre studies through the BMT CTN is anticipated. Those results, along with the ongoing randomised trial of immunosuppressive therapy versus transplantation in paediatric patients with severe aplastic anaemia[32] will determine whether this approach is appropriate for patients at the time of initial diagnosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Support for this clinical trial was provided to the BMT CTN by a grant (U01HL069294) from the National Heart, Lung, and Blood Institute and the National Cancer Institute, both part of the US National Institutes of Health. The lead centres for accrual included the Sidney Kimmel Cancer Center at the Johns Hopkins University School of Medicine (Baltimore, MD, USA), Medical College of Wisconsin (Milwaukee, WI, USA), Miami Children's Hospital (Miami, FL, USA), Blood & Marrow Transplant Program at Northside Hospital (Atlanta, GA, USA), and City of Hope National Medical Center (Duarte, CA, USA). The protocol team wishes to thank Andrew Dietz for his contributions to planning and preparing this protocol before his move to industry. We also appreciate the role of the Telomere Lab at Johns Hopkins Molecular Diagnostics for performance of the flow cytometry-FISH measurements. Additionally, we are grateful to the patients, their families, and the research staff for the ability to complete this study.

Funding

US National Heart, Lung, and Blood Institute and US National Cancer Institute.

References

1. Bacigalupo A How I treat acquired aplastic anemia. Blood 2017; 129: 1428–36. [PubMed: 28096088]
2. Kim SY, Le Rademacher J, Antin JH, et al. Myelodysplastic syndrome evolving from aplastic anemia treated with immunosuppressive therapy: efficacy of hematopoietic stem cell transplantation. Haematologica 2014; 99: 1868–75. [PubMed: 25107891]
3. Townsley DM, Scheinberg P, Winkler T, et al. Eltrombopag added to standard immunosuppression for aplastic anemia. N Engl J Med 2017; 376: 1540–50. [PubMed: 28423296]
4. Tichelli A, Schrezenmeier H, Socié G, et al. A randomized controlled study in patients with newly diagnosed severe aplastic anemia receiving antithymocyte globulin (ATG), cyclosporine, with or without G-CSF: a study of the SAA Working Party of the European Group for Blood and Marrow Transplantation. Blood 2011; 117: 4434–41. [PubMed: 21233311]
5. Patel BA, Groarke EM, Lotter J, et al. Long-term outcomes in severe aplastic anemia patients treated with immunosuppression and eltrombopag: a phase 2 study. Blood 2022; 139: 34–43. [PubMed: 34525188]
6. Peffault de Latour R, Kulasekararaj A, Iacobelli S, et al. Eltrombopag added to immunosuppression in severe aplastic anemia. N Engl J Med 2022; 386: 11–23. [PubMed: 34986284]
7. Tichelli A, de Latour RP, Passweg J, et al. Long-term outcome of a randomized controlled study in patients with newly diagnosed severe aplastic anemia treated with antithymocyte globulin and cyclosporine, with or without granulocyte colony-stimulating factor: a Severe Aplastic Anemia Working Party Trial from the European Group of Blood and Marrow Transplantation. Haematologica 2020; 105: 1223–31. [PubMed: 31582549]

8. Dehn J, Buck K, Maiers M, et al. 8/8 and 10/10 high-resolution match rate for the Be The Match unrelated donor registry. Biol Blood Marrow Transplant 2015; 21: 137–41. [PubMed: 25307419]
9. Clay J, Kulasekararaj AG, Potter V, et al. Nonmyeloablative peripheral blood haploidentical stem cell transplantation for refractory severe aplastic anemia. Biol Blood Marrow Transplant 2014; 20: 1711–16. [PubMed: 25016195]
10. Esteves I, Bonfim C, Pasquini R, et al. Haploidentical BMT and post-transplant Cy for severe aplastic anemia: a multicenter retrospective study. Bone Marrow Transplant 2015; 50: 685–89. [PubMed: 25730184]
11. DeZern AE, Brodsky RA. Haploidentical donor bone marrow transplantation for severe aplastic anemia. Hematol Oncol Clin North Am 2018; 32: 629–42. [PubMed: 30047416]
12. Bacigalupo A, Giammarco S. Haploidentical donor transplants for severe aplastic anemia. Semin Hematol 2019; 56: 190–93. [PubMed: 31202429]
13. Dezern A, Dorr D, Luznik L, et al. Using haploidentical (haplo) donors and high-dose post-transplant cyclophosphamide (PTCy) for refractory severe aplastic anemia (SAA). Blood 2015; 126 (suppl): 2031 (abstr). [PubMed: 26276665]
14. Dezern AE, Luznik L, Fuchs EJ, Jones RJ, Brodsky RA. Post-transplantation cyclophosphamide for GVHD prophylaxis in severe aplastic anemia. Bone Marrow Transplant 2011; 46: 1012–13. [PubMed: 20838390]
15. DeZern AE, Zahurak ML, Symons HJ, et al. Haploidentical BMT for severe aplastic anemia with intensive GVHD prophylaxis including posttransplant cyclophosphamide. Blood Adv 2020; 4: 1770–79. [PubMed: 32343796]
16. Luznik L, O'Donnell PV, Symons HJ, et al. HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. Biol Blood Marrow Transplant 2008; 14: 641–50. [PubMed: 18489989]
17. Bolaños-Meade J, Fuchs EJ, Luznik L, et al. HLA-haploidentical bone marrow transplantation with posttransplant cyclophosphamide expands the donor pool for patients with sickle cell disease. Blood 2012; 120: 4285–91. [PubMed: 22955919]
18. Marsh JC, Kulasekararaj AG. Management of the refractory aplastic anemia patient: what are the options? Blood 2013; 122: 3561–67. [PubMed: 24052548]
19. Sarmiento M, Ramírez PA. Unmanipulated haploidentical hematopoietic cell transplantation with post-transplant cyclophosphamide in a patient with paroxysmal nocturnal hemoglobinuria and secondary aplastic anemia. Bone Marrow Transplant 2016; 51: 316–18. [PubMed: 26501768]
20. DeZern AE, Zahurak M, Symons H, Cooke K, Jones RJ,Brodsky RA. Alternative donor transplantation with high-dose post-transplantation cyclophosphamide for refractory severe aplastic anemia. Biol Blood Marrow Transplant 2017; 23: 498–504. [PubMed: 28013015]
21. Niederwieser D, Pepe M, Storb R, Loughran TP Jr, Longton G. Improvement in rejection, engraftment rate and survival without increase in graft-versus-host disease by high marrow cell dose in patients transplanted for aplastic anaemia. Br J Haematol 1988; 69: 23–28. [PubMed: 3289603]
22. BMT CTN. Administrative manual of procedures (MOP)/policy guidelines. Chapter 6: adverse event reporting. https://bmtctn.net/administrative-manual-procedures-moppolicy-guidelines (accessed Nov 18, 2021).
23. Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. The 2014 Diagnosis and Staging Working Group report. Biol Blood Marrow Transplant 2015; 21: 389–401. [PubMed: 25529383]
24. Alder JK, Hanumanthu VS, Strong MA, et al. Diagnostic utility of telomere length testing in a hospital-based setting. Proc Natl Acad Sci USA 2018; 115: E2358–65. [PubMed: 29463756]
25. Dufour C, Pillon M, Sociè G, et al. Outcome of aplastic anaemia in children. A study by the severe aplastic anaemia and paediatric disease working parties of the European group blood and bone marrow transplant. Br J Haematol 2015; 169: 565–73. [PubMed: 25683884]
26. Viollier R, Passweg J, Gregor M, et al. Quality-adjusted survival analysis shows differences in outcome after immunosuppression or bone marrow transplantation in aplastic anemia. Ann Hematol 2005; 84: 47–55.

27. Desmond R, Townsley DM, Dumitriu B, et al. Eltrombopag restores trilineage hematopoiesis in refractory severe aplastic anemia that can be sustained on discontinuation of drug. Blood 2014; 123: 1818–25. [PubMed: 24345753]

28. Arcuri LJ, Nabhan SK, Cunha R, et al. Impact of CD34 cell dose and conditioning regimen on outcomes after haploidentical donor hematopoietic stem cell transplantation with post-transplantation cyclophosphamide for relapsed/refractory severe aplastic anemia. Biol Blood Marrow Transplant 2020; 26: 2311–17. [PubMed: 32949751]

29. Wang Y, McReynolds LJ, Dagnall C, et al. Pre-transplant short telomeres are associated with high mortality risk after unrelated donor haematopoietic cell transplant for severe aplastic anaemia. Br J Haematol 2020; 188: 309–16. [PubMed: 31426123]

30. Pierri F, Dufour C. Management of aplastic anemia after failure of frontline immunosuppression. Expert Rev Hematol 2019; 12: 809–19. [PubMed: 31311355]

31. Heslop HE, Stadtmauer EA, Levine JE, et al. Blood and Marrow Transplant Clinical Trials Network State of the Science Symposium 2021: looking forward as the Network celebrates its 20th year. Transplant Cell Ther 2021; 27: 885–907. [PubMed: 34461278]

32. Pulsipher MA, Lehmann LE, Bertuch AA, et al. A study assessing the feasibility of randomization of pediatric and young adult patients between matched unrelated donor bone marrow transplantation and immune-suppressive therapy for newly diagnosed severe aplastic anemia: a joint pilot trial of the North American Pediatric Aplastic Anemia Consortium and the Pediatric Transplantation and Cellular Therapy Consortium. Pediatr Blood Cancer 2020; 67: e28444. [PubMed: 32776425]

Research in context

Evidence before this study

Haploidentical bone marrow transplantation in severe aplastic anaemia historically carried unacceptably high rates of graft-versus-host disease (GVHD) to use this approach in a non-malignant disease. We considered all the evidence in the field of transplantation for non-malignant diseases before undertaking this study. We searched PubMed (in all languages) from Jan 1, 1999, to Dec 30, 2015, for case reports and trials in severe aplastic anaemia and transplantation, using the search terms “aplastic anemia”, “haploidentical”, “conditioning regimen”, “myeloablative”, “cyclophosphamide”, “non-myeloablative”, “reduced-intensity”, “hematopoiesis”. Given the relative disease rarity, there were no formal meta-analyses on the topic. The quality of the evidence was modest, including multiple case series and retrospective series with no randomised prospective controlled trials. Previous noted rates of GVHD were as high as 70%, with overall survival varying from 55% to 67%. For a non-malignant disease such as severe aplastic anaemia, it was considered an undue risk in the bone marrow transplantation community to use alternative donors to treat this condition. There were literature and research advocates in the field calling for prospective trials that used conditioning to facilitate engraftment and robust GVHD prophylaxis regimens to improve bone marrow transplantation outcomes in severe aplastic anaemia with alternative donors.

Added value of this study

This trial adds value to the existing literature through demonstration, in a multicentre setting, of a highly useful andbroadly applicable conditioning regimen and GVHD prophylaxis for haploidentical bone marrow transplantation in severe aplastic anaemia, which resulted in improved overall survival and low rates of GVHD compared with approaches described in previous reports. Additionally, novelty of the regimen combined with adequate bone marrow cell dose allow for sustained engraftment, which has not previously been shown in this setting. This study provides strong evidence for use of post-transplantation cyclophosphamide-based GVHD prophylaxis for patients with severe aplastic anaemia when a haploidentical donor is used.

Implications of all the available evidence

These results, in combination with smaller, single-centre trials previously published in the literature, extend the knowledge of the use of haploidentical bone marrow transplantation with post-transplantation cyclophosphamide in severe aplastic anaemia. Furthermore, an important question for the field is how this approach could be incorporated proactively into the therapeutic algorithm at the time of relapse or refractory disease after immunosuppressive therapy for severe aplastic anaemia. Future research might support incorporation of haploidentical approaches into upfront therapy for severe aplastic anaemia, using the same platform and emphasising graft cell dose.

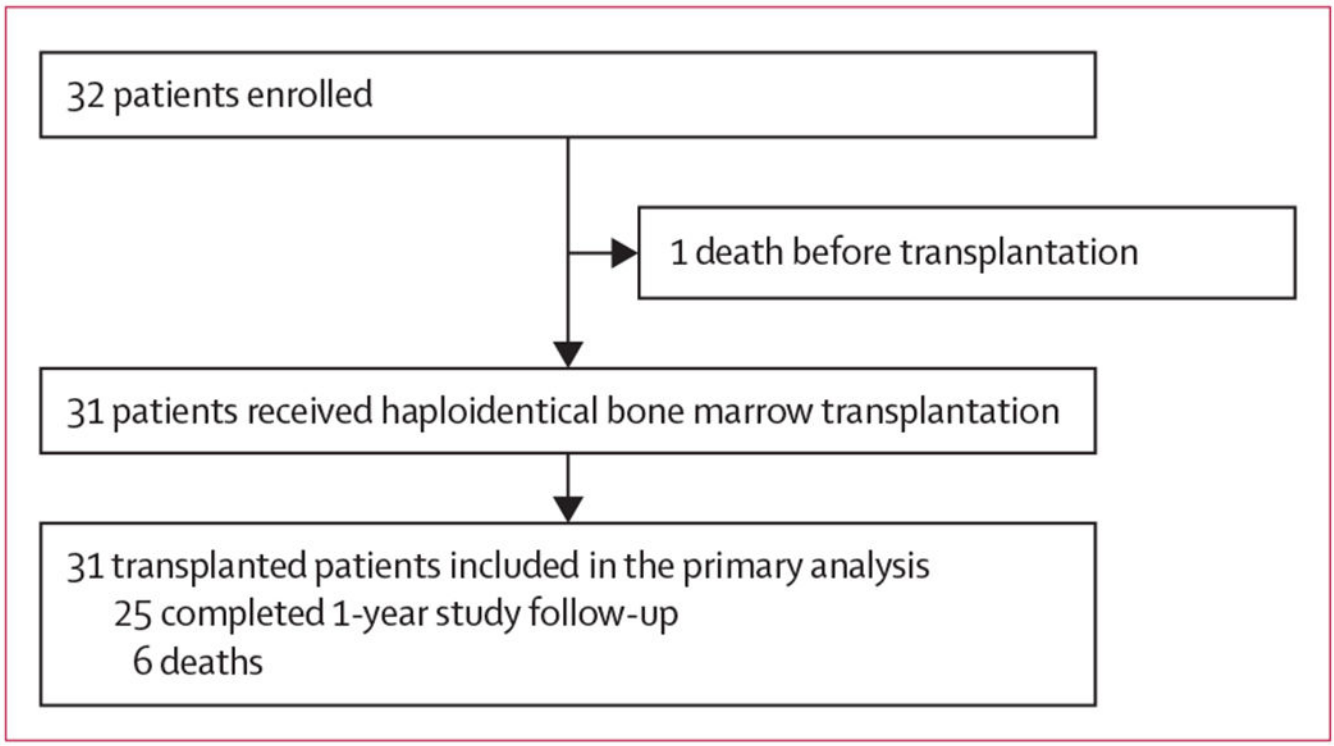

Figure 1: Trial profile

Data regarding number of patients assessed for eligibility and number excluded are not available. The original study design included two cohorts: a haplo-identical bone marrow transplantation group, and an unrelated cord blood group. No patients were enrolled in the unrelated cord blood group so the protocol was revised to remove this group. The unrelated cord blood group was removed from the protocol for version 2.0, which was released on June 19, 2018. The protocol revision was done before any patients were enrolled on the study.

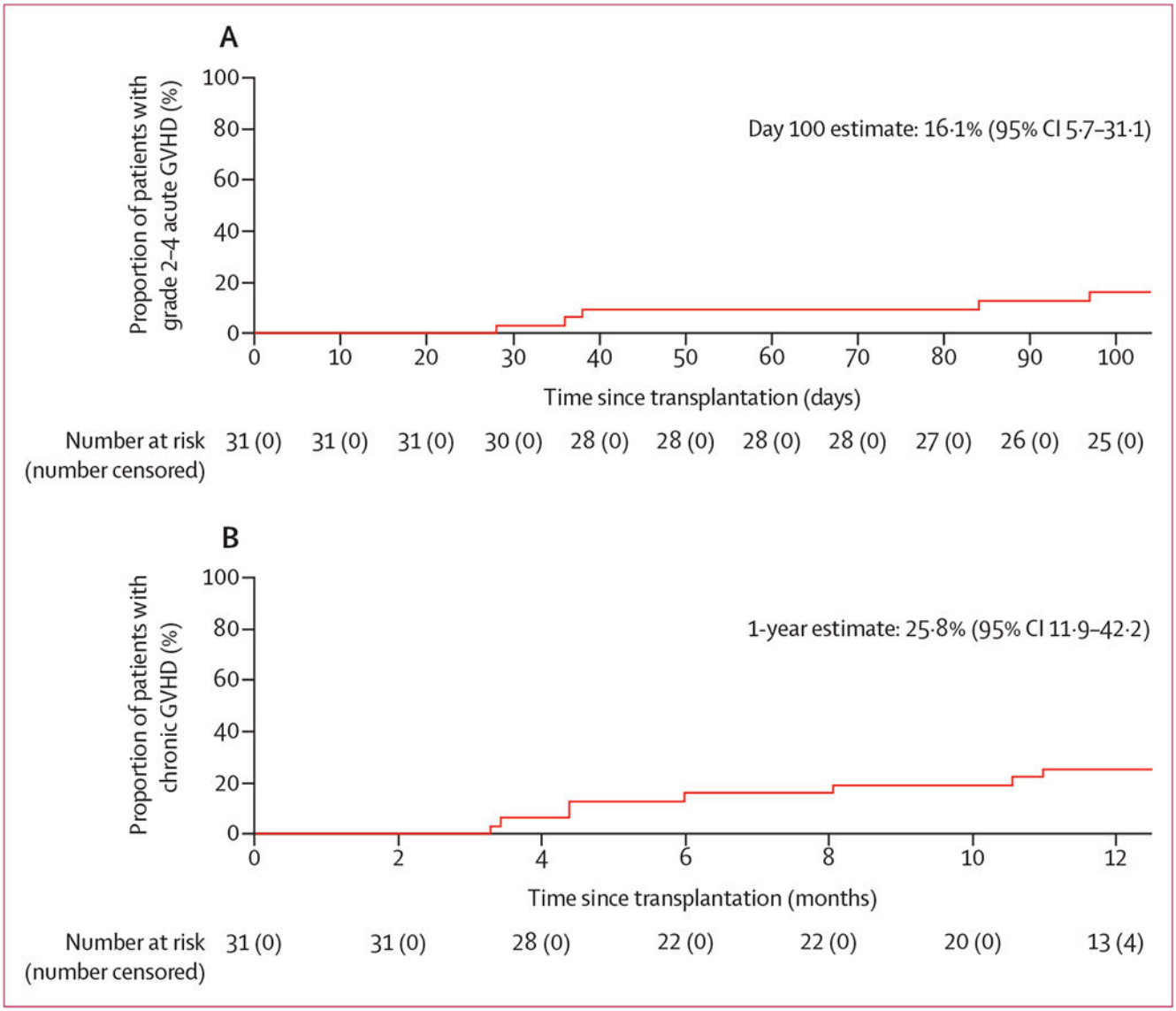

Figure 2: Incidence of acute (grade 2–4) and chronic GVHD

(A) Grade 2–4 acute GVHD. (B) Chronic GVHD. GVHD=graft-versus-host disease. All five cases of grade 2–4 acute GVHD were grade 2.

Table 1:

Baseline characteristics of transplant recipients and haploidentical donors

	Study cohort (n=31)
Sex	
Female	12 (39%)
Male	19 (61%)
Race and ethnicity	
Non-Hispanic White	12 (39%)
Hispanic White	4 (13%)
Non-Hispanic Black	7 (23%)
Hispanic Black	0
Asian or Pacific Islander	5 (16%)
Native American	0
More than one race	1 (3%)
Unknown	2 (6%)
Age, years	24·9 (10·4–51·3)
<10 years	7 (23%)
10–19 years	6 (19%)
20–29 years	5 (16%)
30–39 years	1 (3%)
40–49 years	4 (13%)
50–59 years	2 (6%)
60–69 years	5 (16%)
≥70 years	1 (3%)
Interval from diagnosis to transplantation, months	10·8 (8·1–32·0)
≤6 months	5 (16%)
>6 and ≤12 months	11 (35%)
>12 and ≤18 months	4 (13%)
>18 and ≤24 months	1 (3%)
>24 and ≤30 months	1 (3%)
>30 and ≤36 months	3 (10%)
>36 and ≤42 months	1 (3%)
>42 and ≤48 months	0
>48 and ≤54 months	2 (6%)
>54 and ≤60 months	1 (3%)
>60 and ≤66 months	0
>66 and ≤72 months	0
>72 months	2 (6%)
Donor age, years	38·6 (26·9–46·5)
Donor relationship	

	Study cohort (n=31)
Related haploidentical	31 (100%)
Donor sex	
Female	18 (58%)
Male	13 (42%)
Donor/recipient cytomegalovirus serostatus at baseline	
+/+	17 (55%)
+/−	2 (6%)
−/+	4 (13%)
−/−	7 (23%)
Missing	1 (3%)

Data are n (%) or median (IQR).

Table 2:

Adverse events toxicity and infection summary by system organ class

	Grade 3		Grade 4		Grade 5		Grades 3–5	
	Events	Participants	Events	Participants	Events	Participants	Events	Participants
Abnormal liver symptoms	16	7 (23%)	0	0	0	0	16	7 (23%)
Blood and lymphatic disorders	0	0	1	1 (3%)	0	0	1	1 (3%)
Cardiovascular disorders *	35	15 (48%)	2	2 (6%)	1	1 (3%)	38	15 (48%)
Chemistry/investigations	3	2 (6%)	0	0	0	0	3	2 (6%)
Gastrointestinal disorders	15	9 (29%)	0	0	1	1 (3%)	16	10 (32%)
General disorders	6	4 (13%)	2	1 (3%)	0	0	8	5 (16%)
Haemorrhagic disorders	3	3 (10%)	2	1 (3%)	0	0	5	3 (10%)
Hepatic disorders	8	5 (16%)	2	2 (6%)	0	0	10	6 (19%)
Immune system disorders	0	0	1	1 (3%)	0	0	1	1 (3%)
Infections †	12	7 (23%)	0	0	0	0	12	7 (23%)
Metabolism and nutrition disorders	11	7 (23%)	1	1 (3%)	0	0	12	7 (23%)
Musculoskeletal and connective tissue disorders	1	1 (3%)	0	0	0	0	1	1 (3%)
Nervous system disorders	4	3 (10%)	1	1 (3%)	0	0	5	4 (13%)
Renal disorders	6	4 (13%)	2	1 (3%)	2	2 (6%)	10	5 (16%)
Respiratory, thoracic, and mediastinal disorders	13	8 (26%)	3	3 (10%)	2	2 (6%)	18	8 (26%)
Vascular disorders	0	0	0	0	0	0	0	0
Total (any above events)	133	23 (74%)	17	7 (23%)	6	4 (13%)	156	23 (74%)

Data are n or n (%). The denominator for all percentages is 31 (the total number of participants). Toxicity was as expected per the BMT CTN manual of procedures. The study did not collect data on grade 1–2 toxicities as per the BMT CTN manual of procedures (although grade 2 infection data were collected).

[*] Cardiovascular disorders included sinus tachycardia, heart failure, and pericarditis.

[†] There were a total of 64 infection events in 19 patients, including 52 grade 2 infections in 17 patients. Additional data on infections are shown in the appendix (p 3). Infections were reported whenever an infection event occurred, and infection onset date was also collected.