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Study 275: Updated Expanded Access Program for Remestemcel-L in Steroid-Refractory Acute Graft-versus-Host Disease in Children

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Abstract

Clinical outcomes in children with steroid-refractory acute graft-versus-host disease (SR-aGVHD) are generally poor, with a high mortality rate and limited therapeutic options. Here we report our updated investigational experience with mesenchymal stromal cell (MSC) therapy with remestemcel-L in a multicenter expanded access protocol (ClinicalTrials.gov identifier NCT00759018) in 241 children with aGVHD who failed to respond to steroids with or without other secondary and tertiary immunosuppressive therapies. A total of 241 children with grade B-D SR-aGVHD were enrolled at 50 sites in 8 countries and received 8 biweekly i.v. infusions of human MSCs, 2×10^6 per kg for 4 weeks, with an option for an additional 4 weekly infusions after day +28 for subjects who achieved either a partial response (PR) or mixed response. The mean age of the subjects was 9.6 years; 39% were female, and 60% were white. Most of the subjects had grade C (30%) or grade D (50%) disease, and in most cases, the subjects had failed to respond to other immunosuppressive agents after failing steroids. The primary endpoint was overall response (OR; the sum of complete response [CR] and PR) at day +28. Across all subjects, a 28-day OR was observed in 157 patients (65.1%), with 34 (14.1%) achieving CR and 123

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SUPPLEMENTARY MATERIALS

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(51.3%) achieving PR. Stratified by aGVHD grade at baseline, the OR rate at day +28 was 72.9% for patients with aGVHD grade B, 67.1% for those with aGVHD grade C, and 60.8% for those with aGVHD grade D. Survival through day +100, a secondary endpoint of the study, was 66.9% (n = 160 of 239). Importantly, survival through day +100 was significantly greater in subjects who achieved a day +28 OR compared with nonresponders (82.1% versus 38.6%; $P < .001$, log-rank test). Remestemcel-L safety was generally well tolerated, with no infusional toxicity and no identified safety concerns. In summary, this update to the remestemcel-L expanded access program confirms the reported clinical and survival benefits of remestemcel-L therapy in children with aGVHD who have exhausted all conventional therapeutic options.

Keywords

Remestemcel-L; Mesenchymal stromal cell; Acute graft-versus-host disease; Steroid; Allogeneic hematopoietic cell; transplantation; Compassionate use

INTRODUCTION

Acute graft-versus-host disease (aGVHD), a major obstacle to the success of allogeneic hematopoietic stem cell transplantation (allo-HSCT) and affects 40% to 60% of patients undergoing the procedure. aGVHD is also a major cause of nonrelapse mortality after HSCT [1–3]. Although the management of aGVHD has improved in recent years [4], a therapeutic gap exists in effective management of aGVHD that is refractory to steroid therapy, particularly in subjects with more severe disease, as determined by grade C/D, liver and lower gastrointestinal (GI) organ involvement and/or multiorgan involvement, or high-risk stratification. Failure to respond to initial steroid therapy for aGVHD is associated with mortality as high as 50% to 90% [4–7,8]. There are currently no approved therapies specifically indicated for use in children under age 12 years with steroid-refractory (SR) aGVHD. Recently, ruxolitinib has been approved for use in aGVHD in patients age >12 years; however, the clinical benefit of ruxolitinib in the pediatric population has not been established [9].

Clinical studies of mesenchymal stromal cell (MSC) therapy in patients with SR-aGVHD have demonstrated favorable clinical response rates with an acceptable safety profile [10–13]. The biological and immunosuppressive activity of these cells provides the rationale for investigational use of MSC therapy in aGVHD [14]. MSCs attenuate inflammatory and immunologic processes relevant to aGVHD; they demonstrate immunosuppressive activity in T cell-driven immune responses in animal models of allogenic skin graft rejection and GVHD [15–18]. Specifically, bone marrow-derived MSCs have immunosuppressive and immunomodulatory functions as demonstrated in in vitro and nonclinical studies [16–19]. Allogeneic tolerance, inhibition at immune checkpoints, and paracrine signaling contribute to the potentially beneficial effects of MSCs in aGVHD [19,20].

We previously reported results from 75 subjects treated with remestemcel-L (ex vivo culture-expanded allogeneic adult human MSCs) in a single-arm multicenter expanded access treatment protocol (ClinicalTrials.gov identifier NCT00759018) [21]. Here we report the results in 241 pediatric subjects with SR-aGVHD resistant to multiple

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immunosuppressive therapies (ISTs) who were treated with remestemcel-L under expanded access, including the 75 subjects reported previously.

METHODS

A total of 242 subjects at 50 sites in 8 countries (the United States, Canada, United Kingdom, Italy, Finland, Spain, New Zealand, and Australia) participated in this expanded access program (EAP). The study was approved by the Institutional Review Board or Ethics Committee of each participating institution. The study was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guidelines [22]. Each participant or a legally acceptable representative provided written informed consent. The methodology of this study has been described in detail in the previous publication of the results in 75 subjects [21].

Eligible subjects were age 2 months to 17 years, inclusive, with aGVHD secondary to allo-HSCT or donor lymphocyte infusion who had failed to respond to systemic steroid therapy for grade B-D aGVHD using the Center for International Blood and Marrow Transplant Registry grading scheme [23,24]. Failure to respond to steroid treatment for aGVHD was defined as aGVHD that did not improve after at least 3 days of treatment with methylprednisolone (≥1 mg/kg/day or equivalent). Subjects with a known allergy to bovine or porcine products or evidence of pulmonary infiltrate or diffuse alveolar hemorrhage or likely to require more than 2 L of oxygen by face mask or other delivery method to sustain an O_2 saturation of 92% during the subsequent 3 days were not enrolled. There were no other exclusion criteria established for this protocol. A schematic of the study design is provided in Figure 1.

Investigational Agent

Remestemcel-L is composed of healthy adult human bone marrow-derived MSCs that have been ex vivo cultured and cryopreserved in Plasma-Lyte A Baxter International, USA supplemented with human serum albumin and dimethyl sulfoxide. Each remestemcel-L dose was stored in liquid nitrogen vapor phase until use. On the day of administration, cells were thawed and resuspended in Plasma-Lyte A immediately before administration and administered i.v. over 60 minutes or less.

MSCs are nonhematopoietic cells that express low levels of major histocompatibility complex (MHC) class I molecules, are negative for MHC class II molecules, and are negative for costimulatory molecules CD40, CD80, and CD86. Remestemcel-L cells are $CD105^+$, $CD156^+$, and $CD45^-$; express TNFR1; and suppress IL-2Ra expression on activated lymphocytes. Remestemcel-L cells are manufactured from healthy young bone marrow donors and harvested at passage 5, then cryopreserved as final product. In this study, 11 donors and multiple product lots were used. Most subjects received infusions from more than 1 lot, and some subjects were exposed to cells from more than 1 donor.

Treatment Regimen

Subjects received 8 biweekly i.v. infusions of 2×10^6human MSCs/kg over 4 weeks. Continuing therapy of an additional 4 infusions given weekly were administered to eligible

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subjects. Additional therapy for GVHD was allowed before and concomitant with remestemcel-L treatment. This resulted in the enrollment of a highly pretreated and refractory patient population. This study allowed remestemcel-L administration in addition to each institution's standard of care; accordingly, prophylactic agents and second-line therapies were allowed both before and after initiation of remestemcel-L therapy at the investigators' discretion. However, continuation of additional second-line therapy was not required and could be discontinued at any time.

Patients received all 8 infusions in the initial treatment plan by day +28. Infusions were administered at least 3 days apart. During the course of remestemcel-L treatment, all other aGVHD therapies and any other medications were administered at the discretion of the investigator according to institutional practice.

Subjects were evaluated for efficacy and safety at day +28 and until death, withdrawal, or 100 days after the first infusion (day 0), whichever occurred first. An assessment was performed on day +28 (±2 days) after the first infusion to determine whether continued treatment was indicated. If qualified, the subject was eligible to receive infusions of remestemcel-L (at a dose of 2×10^6 human MSCs/kg) once weekly for an additional 4 weeks. Eligibility for continued treatment was determined by the following:

- If a complete response (CR) was observed, then no additional remestemcel-L infusions were administered.
- If no response (NR) was observed, then no additional remestemcel-L infusions were administered.
- If a partial response (PR) was observed and no safety issues were attributed to remestemcel-L, subjects were eligible to receive continued therapy.
- If a mixed response (MR) was observed and no safety issues were attributed to remestemcel-L, subjects were eligible to receive continued therapy.

Subjects who had an aGVHD flare after achieving a CR and before day +72 were eligible for treatment with remestemcel-L infusions according to the initial treatment plan. Subjects were treated for aGVHD flare once only and not after day +100.

Assessments of Efficacy and Safety

aGVHD assessments were performed at baseline, and subjects were evaluated for efficacy and safety on day +28 and then until death, withdrawal, or +100 days after the first infusion of remestemcel-L (day 0), whichever occurred first. Serious adverse events (SAEs) were defined according to International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use E6 standards [22]. The severity of aGVHD was evaluated using the International Bone Marrow Transplant Registry grading criteria [23,24].

Endpoints

The primary efficacy endpoint was overall response rate (OR), comprising PR and CR, at day +28. Secondary endpoints included survival through day +100, and the relationship between OR on day +28 and OS on day +100 after the first remestemcel-L dose. Additional

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secondary endpoints included further analysis of OR at day +28 and OS at day +100 based on subgroups defined by baseline GVHD grade, organ involvement and a number of demographic and disease characteristics and other subgroup/disease factors.

Safety endpoints included incidence rates and classification of treatment-emergent SAEs, (TESAEs), TESAEs leading to withdrawal, TESAEs leading to death, and TESAEs possibly related to the study drug, as assessed by the investigator. Additional safety endpoints were infusion-related toxicities, relapse of underlying malignancy or leukemic disease, and ectopic tissue formation. Infusional toxicity was evaluated by assessing vital signs and oxygen saturation during and for 2 hours after each remestemcel-L infusion.

Statistical Analysis

The primary objective of this trial was to assess the efficacy of remestemcel-L in improving day +28 OR rate (ORR), an early indicator of subsequent clinical outcomes, in patients with SR-aGVHD. Because this was an EAP, the sample size was not based on any assumptions regarding anticipated treatment effect size. The statistical analyses have been described in detail previously [21].

The primary endpoint and all other efficacy outcomes were evaluated for all enrolled and treated subjects (n = 241), defined as the safety population. One adult (age 32 years) was enrolled but was excluded from the safety and efficacy analyses. For evaluating the primary endpoint, subjects who died, had missing assessment data, received additional aGVHD IST, or withdrew before day +28 were considered nonresponders. For subjects who withdrew from the study because of a TESAE or the need for palliative care owing to a lack of aGVHD response and completed the day +28 endpoint assessment, the 28-day assessment data were used.

Safety outcomes were evaluated for all subjects who received at least 1 dose of remestemcel-L, defined as the safety population. Subgroup analyses included those defined by age, sex, baseline values for aGVHD grade organ involvement, risk stratification, and transplantation characteristics. Categorical variables were summarized as frequency and percentage. Continuous variables were summarized using descriptive statistics (number, mean ± standard deviation, median and range). All confidence intervals had a 95% confidence level. Survival was assessed from initial remestemcel-L treatment to last date of assessment (typically day +100). Kaplan-Meier analyses were used to evaluate overall survival (OS) and the association between day +28 overall response and day +100 survival.

RESULTS

Subjects

Demographic and disease characteristics at baseline are summarized in Tables 1 and 2. The 241 treated subjects included 148 males (61.4%) and 93 females (38.6%), ranging in age from .3 to 18.2 years (median, 9.6 years). Most subjects were white (n = 144; 59.8%) or black/African-American (n = 49; 20.3%) and not of Hispanic or Latino ethnicity (n = 188; 78.0%). The median body weight was 29.4 kg (range, 5.4 kg to 116.9 kg).

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The most frequent underlying malignancies or leukemic disease at transplantation were acute lymphoblastic leukemia and acute myelogenous leukemia (together, n = 54; 22.4%), genetic disease (n = 52; 21.6%), and “other” (n = 47; 19.5%). Of the underlying diseases listed as genetic or “other,” the most frequent were aplastic anemia or severe aplastic anemia (n = 18), sickle cell anemia or sickle cell disease (n = 15), Diamond-Blackfan anemia (n = 6), and beta thalassemia (n = 5). Subjects underwent HSCT between the years 2004 to 2014. The HSCT source was bone marrow in 108 subjects (44.8%), cord blood in 74 subjects (30.7%), peripheral blood stem cells in 49 subjects (20.3%), and donor lymphocyte infusion in 8 subjects (3.3%). A total of 204 subjects (84.6%) received a transplant from an unrelated donor. One hundred sixty-two subjects (67.2%) received myeloablative conditioning, and 58 (24.1%) received a reduced intensity regimen. The median time from HSCT to aGVHD onset was 32.0 days, with an additional median of 23.0 days from the time of aGVHD onset to start of remestemcel-L treatment (range, 5 to 325 days).

The majority of subjects (n = 190; 78.8%) were classified as having high-risk aGVHD based on the Minnesota risk score [25]. At the time of diagnosis, aGVHD was severe (grade C or D) in 160 subjects (66.4%). At the time of the first remestemcel-L treatment (day 0; baseline), 193 (80.1%) had severe disease, as characterized by grade C or D aGVHD. One hundred twenty-one subjects (50.2%) had involvement of 2 or 3 organs. Of the 120 subjects (49.8%) with single organ involvement, 92 (38.2%) had GI only involvement, 23 (9.5%) had skin only involvement, and 5 (2.1%) had liver only involvement. Of the 114 subjects with any skin involvement, 53 (46.5%) had stage 3 or 4 disease; of the 208 subjects with any GI involvement, 158 (76.0%) had stage 3 or 4 disease; and of the 66 subjects with any liver involvement, 29 (43.9%) had stage 3 or 4 disease.

Previous medications received for aGVHD treatment are summarized in Table 3. Subjects were heavily pretreated before initiation of remestemcel-L, with 190 (78.8%) receiving 3 or more nonsteroidal aGVHD therapies. Only 2 subjects had failed steroid therapy only, which clearly demonstrates that the study population was highly refractory to multiple therapies. The most frequently used aGVHD medications (other than steroids) before the first remestemcel-L infusion were tacrolimus (71.0%), mycophenolate mofetil (61.0%), cyclosporine (48.5%), infliximab (36.1%), budesonide (34.0%), methotrexate (15.8%), and etanercept (13.7%).

Any steroid therapy received before the study treatment was recorded. The median duration of steroid therapy was 32.0 days (range, 5 to 325 days; mean, 50.4 ± 53 days), and 53.1% received steroids for more than 28 days.

Subject Disposition

A total of 242 subjects were enrolled in MSB-GVHD275 between 18 August 2007 and 30 March 2015, and 232 subjects (96.3%) completed participation in the protocol. Eight subjects did not complete the protocol, 1 subject was lost to follow-up, and a 32-year old subject was enrolled but excluded from all analyses because he was not a pediatric subject. In addition, data from 8 subjects who re-enrolled in the study were also excluded. Subjects who died during the study were considered to have completed the study.

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A total of 77 subjects (32%) died during the 100-day treatment and follow-up period. Two additional subjects died before the first remestemcel-L treatment, and 2 subjects died outside the +100 day treatment period (1 on day +141 and the other on day +133). None of the treatment-emergent SAEs (TESAEs) that led to death were attributed to remestemcel-L treatment by the investigator. Of the 8 subjects (3.3%) who did not complete the protocol, 4 (1.7%) discontinued the protocol due to TESAEs associated with their underlying disease: recurrent acute lymphoblastic leukemia in 1 subject, acute respiratory distress in 1 subject, and aGVHD in 2 subjects. Four subjects did not complete the protocol for other reasons; 1 subject withdrew from the protocol because the investigator suspected respiratory distress secondary to transplantation, 2 subjects withdrew and transferred to palliative care, and 1 subject withdrew consent following a reported SAE of pneumatosis intestinalis. None of the withdrawals or premature discontinuations were deemed by the investigators to be causally related to remestemcel-L treatment.

Exposure

Subjects received a median of 11 infusions (range, 1.0 to 24.0) and had a median exposure of 46.0 days. One hundred and three subjects (42.7%) received ≤8 infusions, 113 subjects (46.9%) received 8 to 12 infusions, and 25 subjects (10.4%) received >12 infusions.

Efficacy

Results for the primary efficacy endpoint, overall response (OR) to remestemcel-L treatment at day +28, are shown in Table 4. Responders were defined as subjects with an OR (CR or PR) at day +28. Subjects who died on or before day +28 were considered nonresponders. A total of 156 subjects (65.1%) treated with remestemcel-L achieved OR at day +28, with 34 (14.1%) achieving CR and 123 (51.0%) achieving PR (Table 4). Stratified by aGVHD grade at baseline, response rates were 72.9% (n = 35) for grade B, 67.1% (n = 49) for grade C, 60.8% (n = 73) for grade D, and 63.2% (n = 122) for grade C/D combined. Stratified by baseline risk category, standard-risk subjects included day +28 overall responders (70.6%) and 15 nonresponders (29.4%). The high-risk subjects included 121 responders (63.7%) and 69 nonresponders (36.3%). The ORR at day +28 was consistent across baseline organ involvement: 68.4% (78 of 114) in subjects with skin aGVHD, 64.9% (135 of 208) in subjects with any GI aGVHD, and 62.1% (41 of 66) in those with liver aGVHD. Response at day +28 was observed across all subgroups of previous duration of steroid therapy: 1 to 14 days, 74.4%; 15 to 28 days, 55.7%; and >28 days, 67.2%.

ORRs by demographic and GVHD characteristics are provided in Supplementary Table S1. The ORR was significantly higher in subjects age <10 years (71.2%; n = 89) compared with those age ≥10 years (58.6%; n = 68; $P = .041$).

The ORR at day +28 was also consistent between subjects who were started on a nonsteroidal GVHD treatment between the time of initial diagnosis and first remestemcel-L infusion and those who were not (65.6% versus 61.5%). The assessment of OR at day +100 (Table 4) included all subjects who received at least 1 infusion of remestemcel-L and were alive at day +100. Overall response at day +100 was achieved by 51.5% (n = 124) of the

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subjects, with 32.8% achieving a CR (Table 4). A total of 90 subjects (46.6%) with grade C or D disease were responders at day +100.

Effect of Continued Therapy

Overall, 123 subjects with a PR were eligible for continued remestemcel-L therapy. Among those with a PR at day +28, 105 (85.4%) received additional therapy. In those 105 subjects, day +100 response improved to CR for 37 (35.2%), remained PR for 33 (31.4%), and worsened to MR or NR for 32 (30.5%). In contrast, for the 18 subjects with a PR at day +28 who did not receive additional therapy, day +100 response improved to CR in 6 (33.3%), remained PR in 5 (27.8%), and deteriorated in 7 (39.0%). For the 18 subjects with MR at day +28 who received additional therapy, day +100 response improved to OR for 6 (33.3%; 3 CR and 3 PR), remained MR in 4 (22.25), and worsened to NR in 8 (44.4%). Among the 11 subjects with MR who did not receive additional therapy, 2 (18.2%) improved to OR at day +100 (1 CR and 1 PR) and 9 (81.8%) deteriorated to NR at day +100.

Survival

Secondary endpoints in this study included survival through day +100 after the first remestemcel infusion and the relationship between OR on day +28 and survival at day +100. Overall, 160 subjects (66.9%) survived through day +100. Of the 156 subjects who achieved OR at day +28, 128 (82.1%) survived to at least 100 days after the first infusion, compared with 32 of the 83 subjects (38.6%) who did not achieve an OR at day +28 ($P<.001$, Cochran-Mantel-Haenszel test, stratified by baseline GVHD grade). Figure 2 shows day +100 survival (percentage of subjects) by day +28 OR in all subjects and by strata of aGVHD grade and Minnesota risk category. The predictive value of day +28 OR was consistent across aGVHD grades and risk categories (Figure 2). Kaplan-Meier plots of OS through day +100 are shown in Figure 3 stratified by day +28 overall responder or nonresponder status, aGVHD grade, and baseline risk category. As shown in Figure 3A, day +28 ORR was highly predictive of day +100 OS. OS from the start of remestemcel-L treatment stratified by aGVHD grade (Figure 3B) showed robust survival across all aGVHD grades but greater survival at day +100 in subjects with grade B aGVHD compared with those with more severe grades. Stratified by high or standard risk, OS at day +100 (Figure 3C) appeared comparable in subjects with high risk and those with standard risk. There was a significant difference in the probability of survival with increasing disease severity ($P = .0007$); day +100 survival was 81.3% for subjects with grade B disease at baseline, 75.3% for grade C, and 55.9% for grade D disease.

Safety

A summary of safety is provided in Table 5. A total of 296 TESAEs were reported, with more than one half of the subjects (54.4%; n =131) experiencing at least 1 TESAE. Seventy-seven subjects (32.0%) experienced TESAEs leading to death, consistent with aGVHD. The most frequently reported TESAEs leading to death in at least 3% of subjects were respiratory disorders (9.1%), general disorders and administration site conditions (7.5%), infections and infestations (6.6%), and immune system disorders (3.3%). The causes of death by system organ class (SOC) are summarized in Supplementary Table S2. Most TESAEs were deemed unrelated to remestemcel-L therapy; 11 subjects (4.6%) experienced

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12 events that were considered possibly related to remestemcel-L by the investigators. The most frequent TESAEs possibly related to remestemcel-L were respiratory/pulmonary disorders (4 subjects, 2 with respiratory failure) and hypertension (3 subjects). One subject (0.4%) experienced 2 infusion-related reactions. Four subjects withdrew from with study due to TESAEs. Twenty-six subjects (10.8%) discontinued treatment due to a total of 38 TESAEs but remained in the study; 4 of these events were considered possibly related to remestemcel-L treatment. The most frequently reported TESAEs by SOC were infections or infestations (22%; n = 53); respiratory, thoracic, and mediastinal disorders (15.4%; n = 37); general disorders (10.8%; n = 26); and GI disorders (9.1%; n = 22).

Overall, there were no trends of abnormal safety signals related to vital signs, physical findings, or other safety observations in subjects treated with remestemcel-L. Adverse events of special interest in this study were infusion-related toxicity and ectopic tissue formation. One subject experienced 2 infusion-related reactions and discontinued treatment. The first infusion reaction resolved without sequelae; the second, occurring 5 days after the first event, was characterized by fever, decreased blood pressure, and tachypnea. This event also resolved without sequelae, and both events were deemed possibly related to treatment by the investigator.

With respect to potential ectopic tissue formation after treatment with remestemcel-L, 1 subject had findings in the chest, abdominal, and pelvic areas that were attributed to increased thickening of intra-abdominal fat tissue and were considered unremarkable, based on computed tomography scan results. A second case involved 2 nodules in the left lung, which were later considered a sign of fungal infection. Both cases were considered unrelated to remestemcel-L and not clinically significant.

Four subjects had relapse of their underlying malignancy or leukemic disease during the study; none of these was considered related to remestemcel-L. In summary, overall, remestemcel-L was well tolerated in this highly morbid and heavily immunosuppressed study population. No clear safety signals were identified in this study.

DISCUSSION

This report describing the 241 children treated with remestemcel-L under an EAP access treatment protocol provides insight into the efficacy and safety of remestemcel-L as salvage therapy for SR and/or multidrug-resistant aGVHD. An OR was evident within all aGVHD grades, across baseline organ involvement and Minnesota risk categories, and was consistent across subgroups based on race and sex, but was significantly greater in younger children compared with older children. An OS at day +100 of 66.9% was strongly associated with the observed day +28 OR; subjects who responded to remestemcel-L therapy at day +28 had significantly greater survival at day +100 compared with nonresponders at day +28 (82.1% versus 28.6%; $P = .001$, log-rank test) (Figures 2 and 3A). This confirms the highly predictive value of the day +28 response for survival in patients treated with remestemcel-L.

These results are consistent with our previous report of this EAP in the initial 75 children treated [21] and demonstrate clinical effectiveness in the most severely affected aGVHD

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subjects for whom remestemcel-L was used on a compassionate basis when other available therapeutic options were exhausted. The safety profile observed in these 241 subjects indicated that remestemcel-L is well tolerated, consistent with previous observations. The study achieved its primary objectives, demonstrating a 65.1% OR in SR-aGVHD pediatric subjects at day +28. OS at day +100 was 66. 9%. The OS reported in 2 recent observational studies in children with SR-aGVHD was 32% to 35% over 2 years [7,8]. However, it is important to note that in the observational study reported by Rashidi et al [7], despite the relatively low response at day +28, OS data at days +90 to +100 in patients who responded to second-line therapy were similar to our results. The safety and efficacy findings in our series of pediatric subjects are consistent with the observed effects of remestemcel-L treatment in SR-aGVHD in a pediatric subgroup of a randomized, placebo-controlled trial (Study 280) and as first-line therapy in a single-arm phase 3 clinical trial (MSB-GVHD001) [26,27].

In view of the refractory nature of this population and the severity of their aGVHD, these observed effects are consistent across the present study and the 2 studies noted above. That is, in severe SR-aGVHD in pediatric subjects and regardless of numerous other ISTs, there is consistent efficacy of day +28 response and OS at day +100. Moreover, the safety profile of remestemcel-L was consistent across these trials. Remestemcel-L was well tolerated in these gravely ill children with no identified safety concerns.

In the present study and previous remestemcel-L trials in aGVHD, no concerns were identified with respect to adverse events of special interest, including infusion-related toxicities and ectopic tissue formation.

Limitations of this study include the lack of a placebo control group against which to assess the efficacy and safety of remestemcel-L, the assessment of survival only through day +100, lack of retained blood or tissue samples to provide further insight into the mechanism of action of remestemcel-L, and the wide variety of previous and concomitant aGVHD therapies and ISTs. The possibility that some patients might have responded to other concomitant therapies rather than remestemcel-L cannot be excluded. The clinical response and survival observed in the present study are consistent with the results in the pediatric subgroup (n = 28) of a randomized, placebo-controlled study of remestemcel-L: OR at day +28, 64% versus 36%; day +100 survival, 79% versus 50% in the remestemcel-L and placebo groups, respectively [27]. It is important to consider that for most of the 241 subjects enrolled in this program, remestemcel-L was used as a rescue therapy when numerous other agents had failed. Previous and concomitant medications were administered according to institutional policies and physician discretion and thus approximated clinical practice. Although the lack of 1- or 2-year survival is a major limitation of our study, despite this limitation, clinical benefits of remestemcel-L treatment were observed, and no treatment-related toxicities or safety concerns were identified. Moreover, in the context of the current standard of care for SR-aGVHD in children as reported in observational studies and registry data, our findings suggest substantial clinical response and survival through day +100. Future translational studies including biomarkers, tissue sampling, and biodistribution studies may provide additional insight into the biological basis of the observed clinical effects of remestemcel-L in the present study and other published reports.

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Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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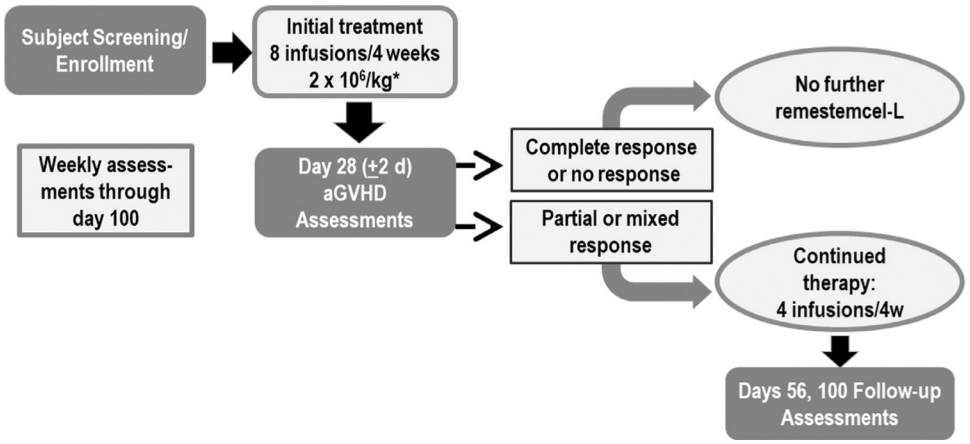

Figure 1.
Schematic of the study design.

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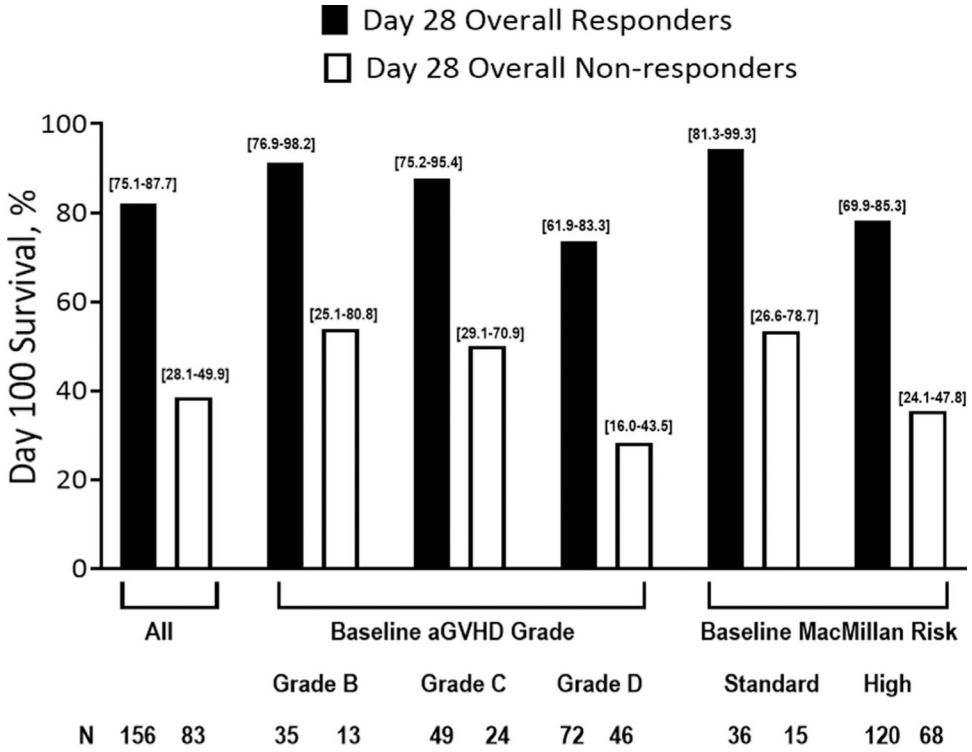

Figure 2.

OS (% of subjects) through day +100 by day +28 overall responders or nonresponders in all subjects, subgroups based on baseline aGVHD grade and subgroups based on baseline MacMillan risk score. Values are percentage of subjects and 95% confidence interval.

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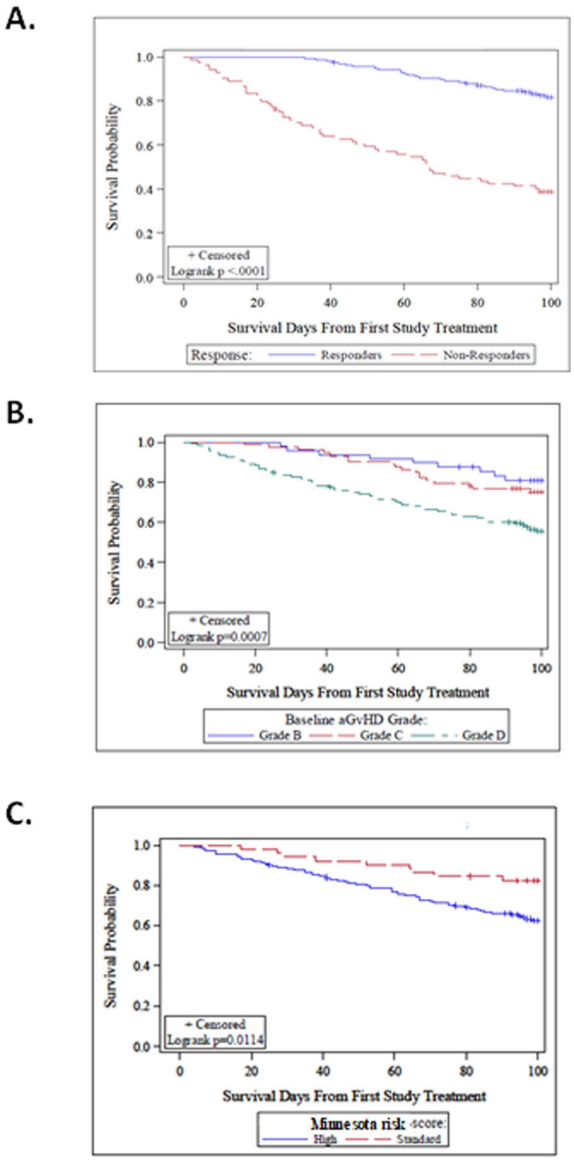

Figure 3.

Kaplan-Meier OS curves through day +100. (A) Stratified by day +28 overall responders or nonresponders. (B) Stratified by baseline aGVHD grade. (C) Stratified by baseline Macmillan risk score.

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Table 1

Summary of Demographic Characteristics (N = 241)

Characteristic	Value
Age, yr *	
Mean ± SD	9.6 ± 5.49
Median (range)	9.6 (.3–18.2)
Sex, n (%)	
Male	148 (61.4)
Female	93 (38.6)
Ethnicity, n (%)	
Hispanic or Latino	45 (18.7)
Not Hispanic or Latino	188 (78.0)
Not reported or missing	8 (3.3)
Race, n (%)	
American Indian or Alaskan Native	3 (1.2)
Asian	12 (5.0)
Black or African American	49 (20.3)
White	144 (59.8)
Other	33 (13.7)
Height, cm (N = 234)	
Mean ± SD	128.6 ± 33.32
Median (range)	128.4 (33.0–184.7)
Weight, kg	
Mean ± SD	34.6 ± 21.14
Median (range)	29.4 (5.4–116.9)

Percentages are based on the number of subjects in the Safety population.

* Age is from the date of enrollment.

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Table 2

Baseline Disease Characteristics, Transplantation and GVHD History (N = 241)

Parameter	Value
Underlying malignancy or leukemic disease at transplantation, n (%)	
Acute lymphoblastic leukemia	54 (22.4)
Acute myelogenous leukemia, primary	54 (22.4)
Chronic myelogenous leukemia	6 (2.5)
Myelodysplastic syndrome	20 (8.3)
Non-Hodgkin lymphoma	6 (2.5)
Hodgkin lymphoma	2 (.8)
Genetic disease *	52 (21.6)
Other *	47 (19.5)
Donor compatibility/donor type, n (%)	
Matched/related	22 (9.1)
Mismatched/related	14 (5.8)
Unrelated	204 (84.6)
Missing	2 (.8)
Stem cell source, n (%)	
Bone marrow	108 (44.8)
Cord blood	74 (30.7)
DLI	8 (3.3)
PBSCs	49 (20.3)
Missing	2 (0.8)
Conditioning regimen, n (%)	
Myeloablative	162 (67.2)
Reduced intensity	58 (24.1)
Nonmyeloablative	17 (7.1)
Missing	4 (1.7)
Grade of aGVHD at diagnosis, n (%)	
Grade A	10 (4.1)
Grade B	70 (29.0)
Grade C	96 (39.8)
Grade D	64 (26.6)
Missing	1 (0.4)
Grade of aGVHD at baseline, n (%)	
Grade B	48 (19.9)
Grade C	73 (30.3)
Grade D	120 (49.8)
Organ staging at baseline (skin), n (%) *	

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Parameter	Value
Stage 0	127 (52.7)
Stage 1	28 (11.6)
Stage 2	33 (13.7)
Stage 3	38 (15.8)
Stage 4	15 (6.2)
Organ staging at baseline, lower GI, n (%)*	
Stage 0	33 (13.7)
Stage 1	24 (10.0)
Stage 2	26 (10.8)
Stage 3	52 (21.6)
Stage 4	106 (44.0)
Organ staging at baseline, liver, n (%)	
Stage 0	175 (72.6)
Stage 1	19 (7.9)
Stage 2	18 (7.5)
Stage 3	18 (7.5)
Stage 4	11 (4.6)
Organ involvement, n (%)†	
One organ	120 (49.8)
Skin	23 (9.5)
Lower GI	92 (38.2)
Liver	5 (2.1)
Two organs	91 (37.8)
Three organs	30 (12.4)
MacMillian Risk Score, n (%)	
High	190 (78.8)
Standard	51 (21.2)
Time from HSCT to aGVHD onset, d (N = 238)	
Mean ± SD	68.0 ± 137.11
Median (range)	32.0 (6.0–1840.0)
Time from aGVHD onset to start of study treatment, d (N = 240)	
Mean ± SD	40.4 ± 45.59
Median (range)	23.0 (1.0–328.03)

DLI indicates donor leukocyte infusion; PBSCs, peripheral blood stem cells. Percentages are based on the number of subjects in the Safety population. Baseline is defined as the last observation before the first infusion, including screening where applicable.

*Ninety-nine subjects had genetic diseases (MedDRA SOC = congenital, familial, and genetic disorders) recorded as “genetic disease” or “other.”

†Involvement of an organ is based on the nonzero stage at baseline.

[≠]One subject started study treatment with only 1 day between GVHD biopsy-confirmed diagnosis and first infusion; however, this subject had started steroid therapy 2 mg/kg on May 1 (9 days before the first treatment) based on clinical presentation (rash). The patient's symptoms continued to worsen, and a skin biopsy confirmed GVHD on May 9; treatment was started on May 10.

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Table 3

Previous Medications for GVHD Treatment and Additional GVHD Therapies Started on or after the First Remestemcel-L Infusion (Day 0) (N = 241)

	Number (%)
Previous medications for aGVHD treatment	
Previous aGVHD treatments, n (%) [*,†]	
Systemic steroids only	2 (0.8)[‡]
One nonsteroidal agent	15 (6.2)
Two nonsteroidal agents	34 (14.1)
Three or more nonsteroidal agents	190 (78.8)
Previous GVHD medications (used in ≥5% of subjects)[‡]	
Methylprednisolone	200 (83.0)
Tacrolimus	171 (71.0)
Mycophenolate mofetil	147 (61.0)
Cyclosporin	117 (48.5)
Infliximab	87 (36.1)
Budesonide	82 (34.0)
Prednisone	62 (25.7)
Methylprednisolone Sodium Succinate	53 (22.0)
Methotrexate	38 (15.8)
Etanercept	33 (13.7)
Sirolimus	31 (12.9)
Beclometasone	30 (12.4)
Daclizumab	25 (10.4)
Triamcinolone	20 (8.3)
Prednisolone	19 (7.9)
Rituximab	18 (7.5)
Basiliximab	17 (7.1)
Antithymocyte globulin	16 (6.6)
Hydrocortisone	13 (5.4)
Other chemotherapeutics	13 (5.4)
Pentostatin	13 (5.4)
Most frequent additional GVHD therapies used from days 0 through +28 inclusive[†,§]	
Tacrolimus	104 (43.2)
Mycophenolate mofetil	51 (21.2)
Infliximab	35 (14.5)
Cyclosporine	28 (11.6)
Sirolimus	21 (8.7)

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	Number (%)
Etanercept	19 (7.9)
Extracorporeal photopheresis	12 (5.0)
Basiliximab	6 (2.5)
Daclizumab	5 (2.1)
Rituximab	5 (2.1)
Antithymocyte globulin	5 (2.1)

Baseline is defined as the last observation before the first remestemcel-L infusion.

[*] Treatments provided before the first remestemcel-L dose date are included.

[†] Previous steroid duration is calculated using first recorded start date, end date, and date of first dose of study medication.

[‡] Subjects may have used more than 1 agent.

[§] Most frequent is defined as 5 or more subjects.

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Table 4

Overall Response at Days +28 and +100 by Baseline aGVHD Grade

Parameter	aGVHD[†] Grade B (N=48)	aGVHD Grade C (N = 73)	aGVHD Grade D (N = 120)	aGVHD Grade C/D (N = 193)	Overall (N = 241)
Response at day +28[*], n (%)					
OR[‡]	35 (72.9)	49 (67.1)	73 (60.8)	122 (63.2)	157 (65.1)
CR	13 (27.1)	11 (15.1)	10 (8.3)	21 (10.9)	34 (14.1)
PR	22 (45.8)	38 (52.1)	68 (56.7)	106 (54.9)	123 (51.0)
Nonresponse	13 (27.1)	24 (32.9)	47 (39.2)	71 (36.8)	84 (34.9)
P value[§]					.305
Response at day +100, n (%)					
OR	34 (70.8)	42 (57.5)	48 (40.0)	90 (46.6)	124 (51.5)
CR	28 (58.3)	23 (31.5)	28 (23.3)	51 (54.8)	79 (32.8)
PR	6 (12.5)	19 (26.0)	20 (16.7)	39 (43.7)	45 (18.7)
Nonresponse	14 (29.2)	31 (42.5)	72 (60.0)	103 (53.4)	117 (48.5)
P value					.001

[*] Day +28 includes assessments between days +20 and +38. Subjects who died before completing the day +28 assessment are considered nonresponders.

[†] aGVHD grade is from the baseline assessment.

[‡] Responder is defined as a subject with an OR (CR or PR) at day +28.

[§] *P* value is based on the Cochran-Mantel-Haenszel test to evaluate differences between responder and nonresponder rates after stratifying on baseline aGVHD grade.

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Table 5

Summary of Safety: TESAEs

Parameter	Number of Subjects (%)	Number of Events*
Subjects with at least 1 TESAE	131 (54.4)	296
Subjects with TESAEs leading to study withdrawal	4 (1.7)	–
TESAE Relationship to study treatment: possibly related†	11 (4.6)	12
Subjects with TESAE leading to treatment discontinuation‡	26 (10.8)	38
Subjects with a TESAE leading to death	77 (32.0)	864
TESAEs by SOC occurring in ≥3% of subjects§		
Infections and infestations	53 (22.0)	
Respiratory, thoracic, and mediastinal disorders	37 (15.4)	
General disorders and administration site conditions	26 (10.8)	
Gastrointestinal disorders	22 (9.1)	
Nervous system disorders	16 (6.6)	
Vascular disorders	14 (5.8)	
Immune system disorders	13 (5.4)	
Renal and urinary disorders	12 (5.0)	
Cardiac disorders	11 (4.6)	

*Number of events includes all occurrences of events.

†As assessed by the investigator.

‡Subjects may continue in the study after treatment is discontinued.

§Subjects reporting more than 1 TESAE within a primary system organ class are counted only once.