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A BMT CTN phase II trial of unrelated donor marrow transplantation for children with severe sickle cell disease

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Key Points

-Children with SCD engrafted unrelated donor marrow after reduced intensity conditioning.

- A high incidence of GVHD and associated mortality compromised safety of the trial.

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Abstract

Children with sickle cell disease (SCD) experience organ damage, impaired quality of life, and premature mortality. Allogeneic bone marrow transplantation from an HLA-matched sibling can halt disease progression but is limited by donor availability.

A multicenter phase II trial conducted from 2008-2014 enrolled 30 children aged 4-19 years; 29 were eligible for evaluation. The primary objective was 1-year event-free survival (EFS) after HLA allele-matched (at HLA-A, -B, -C and –DRB1 loci) unrelated donor transplantation. Conditioning regimen included alemtuzumab, fludarabine, and melphalan. Graft-versus-host disease (GVHD) prophylaxis included calcineurin inhibitor, short course methotrexate and methylprednisolone. Transplant indications included stroke (N=12), trans-cranial Doppler velocity >200 cm/second (N=2), ≥3 vaso-occlusive pain crises/year (N=12) or ≥2 acute chest syndrome episodes (N=4) in the 2 years preceding enrollment. Median follow up was 26 months (range 12–62); graft rejection was 10%. One and 2-year EFS were 76% (95% CI 56–88) and 69% (95% CI, 48–82), respectively. The corresponding rates for overall survival (OS) were 86% (95% CI 67–95) and 79% (95% CI 59-90). The day-100 incidence of grade II-IV acute GVHD was 28% (95% CI 13-45); 1-year incidence of chronic GVHD was 62% (95% CI 41-77); 38% classified as extensive. There were 7 GVHD-related deaths. A 34% incidence of posterior reversible encephalopathy syndrome was noted in the first 6 months. Although the 1-year EFS met the pre-specified target of ≥75%, this regimen cannot be considered sufficiently safe for widespread adoption without modifications to achieve more effective GVHD prophylaxis.

The trial is registered to https://clinicaltrials.gov as NCT00745420.

Introduction

Sickle cell disease (SCD) is a monogenic hemoglobin disorder characterized by hemolytic anemia with variable clinical manifestations following endothelial damage and vasculopathy.[1] Hypoperfusion results in multiple organ damage. In patients with severe disease, symptoms manifest early and progress during childhood. Allogeneic hematopoietic cell transplantation can replace sickle erythropoiesis. The results of Human Leukocyte Antigen (HLA) - matched sibling donor transplantation are excellent with event-free survival (EFS) in excess of 90%, and acceptable rates of graft rejection and graft-versus-host disease (GVHD).[2-5] HLA-matched sibling donor transplants account for the majority of transplants performed worldwide for hemoglobinopathy.[6,7] However only 18% of patients with SCD have an HLA-matched sibling donor in the United States.[8] HLA matched adult unrelated donors (URD) have been used to expand the donor pool for non-malignant hematologic disorders, but their role in SCD transplants is unclear.[9-11] Although the likelihood of finding an HLA-matched unrelated donor for African Americans is low at 16-19%, utilization of these donors does expand the donor pool.[12] To-date, most SCD transplants have used myeloablative conditioning regimens, but these can result in toxicities such as growth inhibition, gonadal hypofunction, and sterility.[13-16] Reduced intensity conditioning (RIC) regimens while associated with a more favorable toxicity profile, can be associated with higher rates of graft rejection (GR), especially with graft sources such as umbilical cord blood.[17-20] A RIC regimen augmented with host immunoablation by alemtuzumab was previously successful in achieving donor engraftment.[21,22] In that report of HLA-matched sibling donor bone marrow transplantation (BMT) in 52 children with hemoglobinopathies,

acute and chronic GVHD rates were 23% and 13% respectively.[21] The regimen was adopted for a phase II URD transplant trial with bone marrow or umbilical cord blood grafts through the Blood and Marrow Transplant Clinical Trials Network (BMTCTN 0601; NCT 00745420). This report describes outcomes from the trial using bone marrow grafts. The umbilical cord blood arm was closed early following a high graft rejection rate.[19]

Methods

Study Design

The primary endpoint was 1-year event-free survival; death from any cause, graft rejection or recurrent disease was considered an event. Pre-specified secondary endpoints included overall survival, hematopoietic recovery, acute and chronic GVHD, infections, hepatic sinusoidal syndrome, interstitial pneumonitis, seizure, posterior reversible encephalopathy syndrome (PRES) and health-related quality of life (HRQL). The trial opened on April 11, 2008 and closed to enrollment on April 24, 2014. Enrollment was paused for clarification of HLA typing requirements once during this period for 6 months. The analysis includes data collected as of March 2016. The median follow up of surviving patients was 26 months (range 12-62). All patients were followed for at least 24 months except for one patient who was lost to follow up at 12 months.

Patients

The protocol was approved by the Institutional Review Board at each of the participating institutions. Informed consent was obtained from parents or patients aged >18 years and assent (age 7-18 years) was obtained prior to enrollment. The consent

form extensively described alternate conservative treatment approaches for SCD as well as the pros and cons of transplant. Trial eligibility was confirmed by 3 independent hematologists. Eligible patients were aged 3.0 - 20 years with severe SCD indicated by one or more the following: 1) clinically significant neurologic event (stroke) or any neurologic defect lasting >24 hours and accompanied by an infarct on cerebral magnetic resonance imaging; 2) transcranial Doppler velocity >200 cm/second by the non-imaging technique or velocity that exceeds 185 cm/second by the imaging technique measured at a minimum of two separate occasions one month or more apart[23]; 3) minimum of two episodes of acute chest syndrome within the preceding 2-year period and defined as new pulmonary alveolar consolidation involving at least one complete lung segment despite adequate supportive care measures; 4) minimum of three new pain events per year in the previous 2 years and defined as new onset of pain lasting for at least 2 hours, for which there was no other explanation, and occurred despite adequate supportive care measures. Adequate organ function pre-transplant required serum creatinine <1.5x upper limit of normal for age and GFR >100 ml/min/1.73 m2 or adjusted for age; ALT and AST <5x the upper limit of normal and direct serum bilirubin <2× upper limit of normal; left ventricular ejection fraction >40% or LV shortening fraction >26%; and DLCO >40% of predicted (corrected for hemoglobin). Patients with serum ferritin >1000 ng/ml were required to have a liver biopsy demonstrating the absence of cirrhosis and bridging fibrosis if they had received regular red cell transfusions for >1 year. Hemoglobin S level was maintained at ≤45% within 7 days of initiation of transplant conditioning and chelation and/or hydroxyurea were discontinued 48 hours prior to initiation of conditioning. Ineligible patients included those

with an HLA-matched sibling, HIV seropositive, performance score <40, and uncontrolled bacterial, viral or fungal infection.

Treatment

The conditioning regimen included alemtuzumab, fludarabine and melphalan, with the alemtuzumab administered between day 22 and 19 prior to graft infusion to achieve host immunoablation (Table I). Prophylaxis for GVHD consisted of a calcineurin inhibitor (tacrolimus or cyclosporine) administered from day 3 through day 100 after graft infusion with subsequent taper through day 180, methotrexate 7.5 mg/m^2 on days 1, 3 and 6, and methylprednisolone 1 mg/kg/day from days 7 through 28 with subsequent taper by 20% per week. Supportive care recommendations included granulocyte colony-stimulating factor commenced on day 7 and continued until an absolute neutrophil count of 1.5 x 10^9/L on three days after the nadir, weekly surveillance for cytomegalovirus (CMV) and Epstein-Barr virus (EBV) reactivation, seizure prophylaxis for the duration of use of calcineurin inhibitors, strict blood pressure control, pre-emptive therapy for viral infections, bacterial prophylaxis through day 100 and prompt treatment of overt or suspected infections. In order to mitigate the risk of intracranial hemorrhage, platelets were maintained ≥50 x 10^9/L.[24]

Outcomes

The primary endpoint was 1-year EFS. Primary or secondary GR or death, were considered events. Primary GR was defined as the presence of < 20% donor cells as assessed by bone marrow or peripheral blood chimerism assays (any lineage) on or after day 42. Secondary GR was defined as the presence of <20% donor derived hematopoietic cells in peripheral blood or bone marrow in a patient with prior evidence

of >20% donor cells. The level was chosen based on absence of SCD symptoms even when donor chimerism in blood or marrow approached 10%.[21,25] Survival was defined as the time from transplantation to death or last follow-up. Neutrophil recovery was defined as the first of 3 days when the absolute neutrophil count (ANC) was ≥0.5 x 10^9/L. Platelet recovery was defined as the first of 7 days without a platelet transfusion that the platelet count was ≥50 x 10^9/L. Acute and chronic GVHD were graded by Seattle (limited/extensive) and NIH criteria (mild/moderate/severe).[26] Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 was used to report expected grade 3–5 adverse events. Major regimen-related toxicity (RRT) was defined as grade 4 or 5 in any organ system or grade 3 for pulmonary, cardiac, renal, central nervous system, oral or mucosal.[27] HRQL was assessed pre-transplant (within 2 months of transplantation), and thereafter on Day 100, 6 months, and 1-year post transplantation using the Child Health Questionnaire (CHQ). The CHQ was chosen as it was the only HRQL measure that was validated and reliable for use in children with SCD at the time the study commenced.[28,29] The CHQ-Parent Form 50 was used for parent reports and the CHQ-Child Form 87, for the child self-report for children 10 years of age or older.

Statistical analysis

The primary hypothesis was that a RIC regimen would be sufficient for stable engraftment after HLA-matched URD BMT and result in 1-year EFS ≥75%. The sample size of 30 patients was chosen based on a 95% confidence interval length of 31%. However, one patient was deemed ineligible after enrollment because the patient and donor were mismatched at 2 HLA-loci. Therefore the analysis includes 29 patients.

EFS and overall survival (OS) were calculated using the Kaplan-Meier estimator.[30] The cumulative incidence method was used to estimate the incidence of events in the presence of competing risks for neutrophil and platelet recovery, and acute and chronic GVHD; in each case, death was considered the competing risk.[31] HRQL measurement was based on the CHQ Parent Form 50 (for patients 5-18 years of age) and the CHQ Child Form 87 (for patients 10-18 years of age). Mean scores for the CHQ were calculated based on a 4-6 point response scale for each item and transformed according to the developer's instructions to a 0-100 scale with a higher score representing a better quality of life.[32] One domain, Change in Health, is composed of 1 question that is reported on a 1-5 point scale with a higher number meaning better health. The impact of a change by >1 point is considered significant on a 5 category scale.[33,34] HRQL data were analyzed for changes in mean HRQL score from pre-transplant measurement and performed as an exploratory analysis given the small sample size. Paired t-test was used to assess changes from baseline to each post-transplant time point (day 100, 6 months and 1-year). Only p values of <0.01 were considered significant for the HRQL analyses given the multiple comparisons. All analyses were performed using SAS version 9.3 (Cary, NC).

Results

Patient and donor characteristics

The characteristics of the donors and 29 patients who met eligibility criteria are shown in Table II. All patients had a hemoglobin SS genotype. The median age at transplant was 14 years (range 6-19) and 53% were male. Indications for transplant included stroke (41%), elevated TCD velocity (7%), recurrent episodes of acute chest syndrome

(14%) or significant pain (41%). Pre-transplant, 26 patients had performance scores of 90 or 100; 2 patients, a score of 80 and the remaining patient, 70. All patients had received erythrocyte transfusions prior to transplantation. The median serum ferritin level was 722 ng/ml (range, 55 – 7324). Eight patients underwent liver biopsy for history of chronic red cell transfusions and a serum ferritin level of >1000 ng/ml but no patient was excluded as none had evidence of bridging fibrosis or liver cirrhosis. The median hemoglobin S percent at transplantation was 20.8 (range 3.9 – 43). All 29 eligible patients received bone marrow grafts from an adult unrelated donor and were HLA-matched at the allele-level at HLA-A, -B, -C and –DRB1. One unrelated adult donor was a carrier with hemoglobin AS genotype. The median total nucleated cell dose of the bone marrow graft was 3.5 x 10^8/kg (range 1.3 – 6.8). The median CD34 dose of the graft was 2.9 x 10^6/kg (range 0.3 – 9.2).

Event-free Survival, Overall Survival, and Engraftment

The primary endpoint was met. One-year event-free survival was 76% (95% CI, 56 - 88) and overall survival was 86% (95% CI, 67 - 95). At data cut-off in March 2016, the 2-year event-free survival was 69% (95% CI, 48 – 82) and overall survival was 79% (95% CI, 59 - 90) (Figures 1A and 1B). Twenty-seven of 29 patients engrafted. The median time to neutrophil recovery was 12 days (range 6-16) and to platelet recovery was 24 days (range 7-90), similar to published results using unrelated donors.[35] Two patients experienced primary GR (day 39 and day 91); 1 patient developed secondary GR on day 48 for a cumulative incidence of GR of 10%. All three patients experiencing GR recovered host hematopoiesis without marrow aplasia. Because mixed chimerism occurs frequently after transplantation for SCD, we evaluated the percentage of donor

cells at 3 months, 1 year, and 2 years.[20,21,25] All engrafted patients demonstrated >90% donor chimerism at 3 months and this persisted at the 1-year and 2-year time-points in evaluable patients (n=22 and n=19 at 1- and 2-years respectively). Hemoglobin S levels were undetectable in all but one patient who received a graft from an unrelated donor with sickle cell trait and the hemoglobin S level was consequently 42%.

Though a RIC regimen was administered, RRT was implicated in 83% of grade 3-5 adverse events (63/76). Ten patients developed PRES with a 1-year incidence of 34% (95% CI 18 – 52), resulting in reiteration of the importance of strict blood pressure control based on lower blood pressure norms established for SCD patients, and correcting any electrolyte imbalance. Two PRES events occurred prior to transplant. In the remaining 8 patients, calcineurin inhibitor was withdrawn. Thereafter, 1 patient received sirolimus, 2 received mycophenolate mofetil, and 5 received no alternate GVHD prophylaxis. Three patients developed renal failure and required dialysis. These events were transient and all patients fully recovered.

Eight patients died after transplantation. Seven patients, all aged $\geq$14 years, died of GVHD and related complications (Table III). Five of the 7 patients had ferritin levels >1000 ng/ml though none had fibrosis or cirrhosis. One patient with primary graft rejection died of infection 3 months after a second myeloablative transplant. Four GVHD-related deaths occurred within the first year after transplantation while three occurred between 507 and 960 days.

Graft-versus-host Disease

The cumulative incidence of grade II-IV acute GVHD on day +100 was 28% (95% CI, 13 – 45) and grade III-IV acute GVHD was 17% (95% CI, 6 - 33) (Figure 2A). The

cumulative incidence of chronic GVHD at 1 year (Figure 2B) was 62% (95% CI, 41- 77) with 38% classified as extensive. By National Institute of Health scoring criteria, chronic GVHD was classified as mild in 6, moderate in 8, and severe in 5 patients. Of the 19 patients with sustained donor engraftment, 4 discontinued immune suppression by 1-year, 6 discontinued in the second year, and 5 discontinued after 2 years. Of the remaining 4 patients, one patient was weaning immune suppression when lost to follow up at 1 year, 2 were weaning post GVHD resolution, and one continued treatment for stable chronic GVHD. Performance scores at the 2-year or last follow up visit were 100 in thirteen patients, 90 in five, and 80 in three patients.

Health Related Quality of Life

SCD adversely affects quality of life as previously reported.[36] We were interested in learning if HRQL improved after unrelated donor BMT in pediatric recipients. Validated measures for HRQL include change in health, physical functioning, behavior, and self-esteem. Parental proxies and patients, who completed the forms, as indicated based on age, reported significant improvements in the change in health domain post-transplant (Table IV). Although initially patients did not report any differences, parent proxies (n=21) reported significantly worse Self Esteem HRQL (mean change -15.12, p=0.006) but significantly better General Health Perception scores (mean change 11.1, p =0.0003) at day 100 compared to pre-transplant baseline. The child reported Change in Health score (n=13) improved by a mean of 1.46 (p=0.0013) at 12 months post-transplant compared to pre-transplant scores. Parental proxies reported similar improvements at 6 and 12 months compared to pre-transplant scores (mean change 1.15 and 1.53 respectively, p=0.001). The limited sample size precluded sub-analyses

such as assessing these changes in patients with and without chronic GVHD (see supplemental table).

Discussion

Although EFS after HLA-matched sibling donor transplantation is greater than 90%, most patients do not have an HLA-matched sibling.[4,5,21,37,38] This is the first multicenter unrelated donor transplant trial for SCD in North America and was conducted to expand access to transplantation utilizing HLA-matched unrelated donors. The RIC regimen of alemtuzumab, melphalan and fludarabine was used to overcome the higher risk of graft rejection with URD BMT while limiting toxicities associated with myeloablative regimens which may be exacerbated in patients with severe SCD and limit patient acceptance.[14,16,39,40]

Although the trial met the pre-specified 1-year endpoint of 75% event-free survival, the 1-year chronic GVHD rate was higher than expected after HLA-matched URD BMT and GVHD was the predominant cause of death, and noted primarily in older patients. Reports in African Americans with severe aplastic anemia, (combining sibling and URD transplants) suggest an overall chronic GVHD rate of 36% (95% CI 24-48) compared to 30% noted in Caucasians (p=0.36), although extensive chronic GVHD was observed more commonly in African-Americans than Caucasians (72% vs. 49%, p=0.06) as was GVHD related mortality.[41] Other than race, additional factors may have influenced the observed high rates of chronic GVHD in this trial. HLA-matching at HLA-DPB1 loci was not considered in donor selection and a mismatch at this locus increases the risk of acute GVHD.[42-44] Another plausible explanation could be the timing of alemtuzumab administration three weeks prior to infusion of the graft (distal administration) to

overcome host rejection of the graft. It was timed to achieve low alemtuzumab levels at the time of graft infusion to maximize donor T cell engraftment, and thus without significant effect as a GVHD prophylaxis agent.[21] Chronic GVHD rates are also expected to be higher in URD BMT and increase with recipient age; the higher rates observed in this trial are consistent with less protection against chronic GVHD.[45-47] Further, the protocol recommended calcineurin inhibitor taper early (after day 100) in the absence of GVHD and may have contributed to de novo chronic GVHD subsequently. Chronic GVHD developed in 8 of 10 patients after they developed PRES symptoms. The protocol did not specify alternate GVHD prophylaxis in the event of PRES and treatment was left to center choice. Since it is common practice to discontinue or modify calcineurin inhibitor use following PRES, it is possible that the withdrawal or modification of the calcineurin inhibitor following the development of PRES may have additionally contributed to GVHD. Alemtuzumab or antihuman T-lymphocyte immune globulin (ATG) used just proximal to transplant can offer better protection against GVHD, but predispose to mixed chimerism and rejection.[48-50] Novel preparative agents such as treosulfan and GVHD prophylaxis methods such as post-transplantation cyclophosphamide have shown recent promise in transplantation for SCD. [51,52]

HRQL improved significantly by one year post-transplant in the areas of 'Change in Health' for these patients compared to pre-transplant scores. Other HRQL domains did not show significance changes from baseline. The significant changes noted here, even in this small sample size, support that these children felt better and reported better functioning overall related to their health after transplant despite the high incidence of

chronic GVHD. We would expect patients with significant chronic GVHD after BMT to experience lower HRQL than those without, but the sample size was too small for a meaningful comparison between the two groups.

No patient developed hepatic sinusoidal syndrome or idiopathic pulmonary syndrome. However, a third of the patients developed PRES (a known complication of SCD and hemoglobinopathy transplants) that was reversible, despite our recommendation for strict blood pressure monitoring and prompt intervention.[53,54] Baseline blood pressure in SCD patients are generally lower than published norms for age, race and sex, and use of corticosteroid and calcineurin inhibitors may have exacerbated this complication.[55,53,56,57]

In conclusion, the trial met its pre-specified 1-year EFS and significantly improved HRQL was reported post-transplant. However, though the RIC provided successful engraftment in the majority, the regimen cannot be considered safe for widespread adoption without modification due to the RRT and high rate of chronic GVHD, which was the predominant cause of mortality. Future trials on URD transplantation for SCD should focus on strategies that minimize risks of GVHD and include stopping rules for chronic GVHD.

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Author Contribution: SS, ME, JAP, BRL, MMH, MW, NK designed the trial, interpreted data and drafted the manuscript. SS, NK, JL, MW and ME adjudicated primary and secondary endpoints. JW prepared the dataset and analyzed data. JAP and BRL prepared and analyzed HRQL data. All other authors critically reviewed the manuscript. All authors approved the final manuscript.

Figure legends:

Figure 1A: The 2-year probablity of event-free survival following unrelated donor transplantation for severe sickle cell disease

Figure 1B: The 2-year probablity of overall survival following unrelated donor transplantation for severe sickle cell disease

Figure 2A: The 100-day probability of acute graft-versus-host disease following unrelated donor transplantation for severe sickle cell disease

Figure 2B: The 1-year probability of chronic graft-versus-host disease following unrelated donor transplantation for severe sickle cell disease

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Table I. Treatment Regimen

Day	Treatment
	Alemtuzumab test dose 3 mg IV*
-22	
-21	Alemtuzumab 10 mg IV*
-20	Alemtuzumab 15 mg IV*
-19	Alemtuzumab 20 mg IV*
-18	
-8	Fludarabine 30 mg/m^2 IV
-7	Fludarabine 30 mg/m^2 IV
-6	Fludarabine 30 mg/m^2 IV
-5	Fludarabine 30 mg/m^2 IV
-4	Fludarabine 30 mg/m^2 IV
-3	Melphalan 140 mg/m^2 IV Cyclopsorine or tacrolimus dosed to maintain appropriate levels through day 100 and then tapered to day 180
-2	Rest
-1	Rest
0	Bone marrow infusion
+1	Methotrexate 7.5 mg/m^2 IV
+3	Methotrexate 7.5 mg/m^2 IV
+6	Methotrexate 7.5 mg/m^2 IV
+7	Methyl prednisolone 1 mg/kg/day IV through day 28 and then taper G-CSF 5 microgram/kilogram body weight/day IV until absolute neutrophil count ≥ 0.5 x 10^9/L for 3 consecutive days

*Alemtuzumab could be administered between day -22 and day -18 but was required to be on 3 consecutive days; test dose of alemtuzumab administered 24 hours prior to 1st dose

Table II. Characteristics of Donors and Recipients

Donor Characteristics	Number
Age, median (range), years	35 (21 – 55)
Race/ethnicity	
Caucasian	11
African American	11
Multirace	5
Not reported	2
Recipient Characteristics	
Age, median (range), years	14 (6 – 19)
Sex	
Male	16
Female	13
Race/ethnicity	
African American	26
Hispanic	3
Indications for transplant*	
Stroke	12
Trans cranial doppler velocity >200 cm/second	2
Acute chest syndrome	4
Vaso-occlusive pain crisis	12
Chronic blood transfusion prior to transplant	14
Performance score	
100	17
90	9
80	2
70	1
Transplant Characteristics	
CMV seronegative donor and recipient	8
CMV seropositive donor and recipient	9
CMV seronegative donor and CMV seropositive recipient	3
CMV seropositive donor and CMV seronegative recipient	9
ABO Blood group matched	15
ABO Blood group major mismatch	9
ABO Blood group minor mismatch	5
Sex matched transplants	15
Female donor, male recipient	7
Male donor, female recipient	7

*some patients had more than 1 indication; CMV- cytomegalovirus

Table III. Cause of Death

#	Age (years)	Time of death (days)	Complications at the time of death
1	17	231	Acute GVHD (gut), opportunistic infection, ARDS
2	16	539	Chronic GVHD, CMV infection, encephalomyelitis, cardiorespiratory failure
3	17	200	Acute GVHD (gut), respiratory and renal failure
4	19	960	Chronic GVHD
5	16	507	Chronic GVHD, VRE and HSV infections
6	14	199	Acute GVHD, Candida and CMV infections, respiratory and renal failure
7	18	143	Acute GVHD (gut), pulmonary hemorrhage, *Staphylococcus aureus* pneumonia

GVHD- graft-versus-host-disease; ARDS-Acute respiratory distress syndrome; CMV-cytomegalovirus; VRE- Vancomycin resistant *enterococcus*; HSV-herpes simplex virus

Table IV. Health Related Quality of Life*: Changes from pre-transplant baseline to day 100, 6 months and 1-year

	Day 100			6 Month			1 Year		
	N	**Mean (SEM)**	**p-value**	**N**	**Mean (SEM)**	**p-value**	**N**	**Mean (SEM)**	**p-value**
Parent proxy									
Self esteem scale score	21	-15.12 (4.89)	0.0057*	20	-11.46 (6.28)	0.0839	15	-3.61 (6.66)	0.5959
General health perception score	21	11.13 (2.51)	0.0003*	20	7.63 (3.31)	0.0326	15	8.89 (5.27)	0.1135
Change in health score	21	0.90 (0.38)	0.0286	20	1.15 (0.36)	0.0052*	15	1.53 (0.48)	0.0062*
Child									
Self esteem scale score	18	-0.59 (4.51)	0.8976	16	-4.33 (5.87)	0.4722	13	4.97 (5.33)	0.3691
General health perception score	18	-1.90 (4.29)	0.6631	16	-6.69 (4.99)	0.2001	13	6.99 (6.35)	0.2927
Change in health score	18	0.33 (0.45)	0.4691	16	0.19 (0.52)	0.7225	13	1.46 (0.35)	0.0013*

*P < 0.01 = statistically significant

Negative mean change denotes worsening HRQL score
Positive mean change denotes improved HRQL score

Other items tested include the following; none of these items reached the level of significance at any of the time points tested:
Physical functioning; social limitations due to emotional difficulties; social limitations due to behavioral difficulties social limitations due to physical health; bodily pain and discomfort; behavioral; mental health; self esteem; emotional impact; time impact; family activities; global health; global behavior; change in health; family cohesion; physical summary; psychosocial summary.

Figure 1A: Event-Free Survival

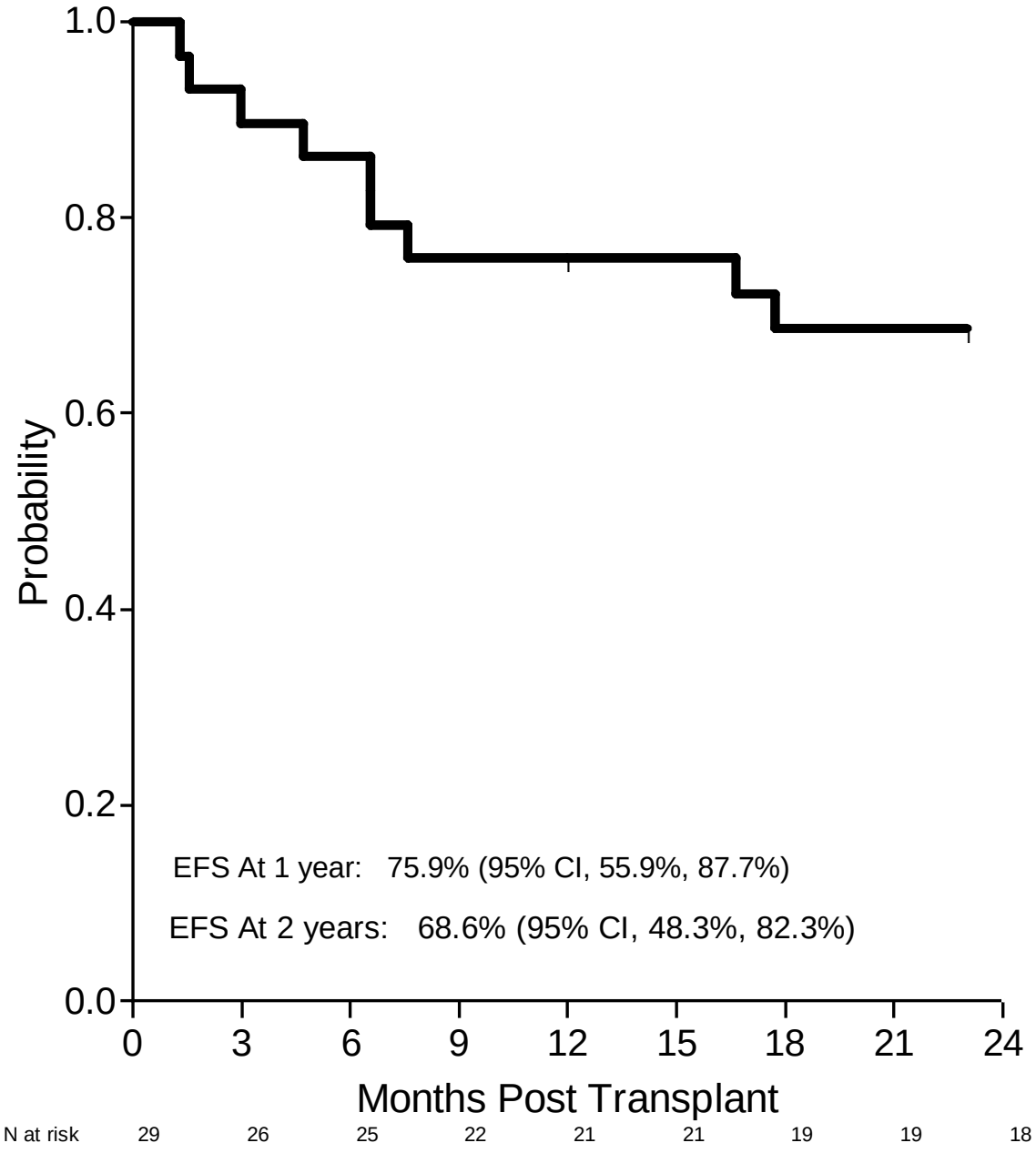


Figure 1B: Two-year Overall Survival

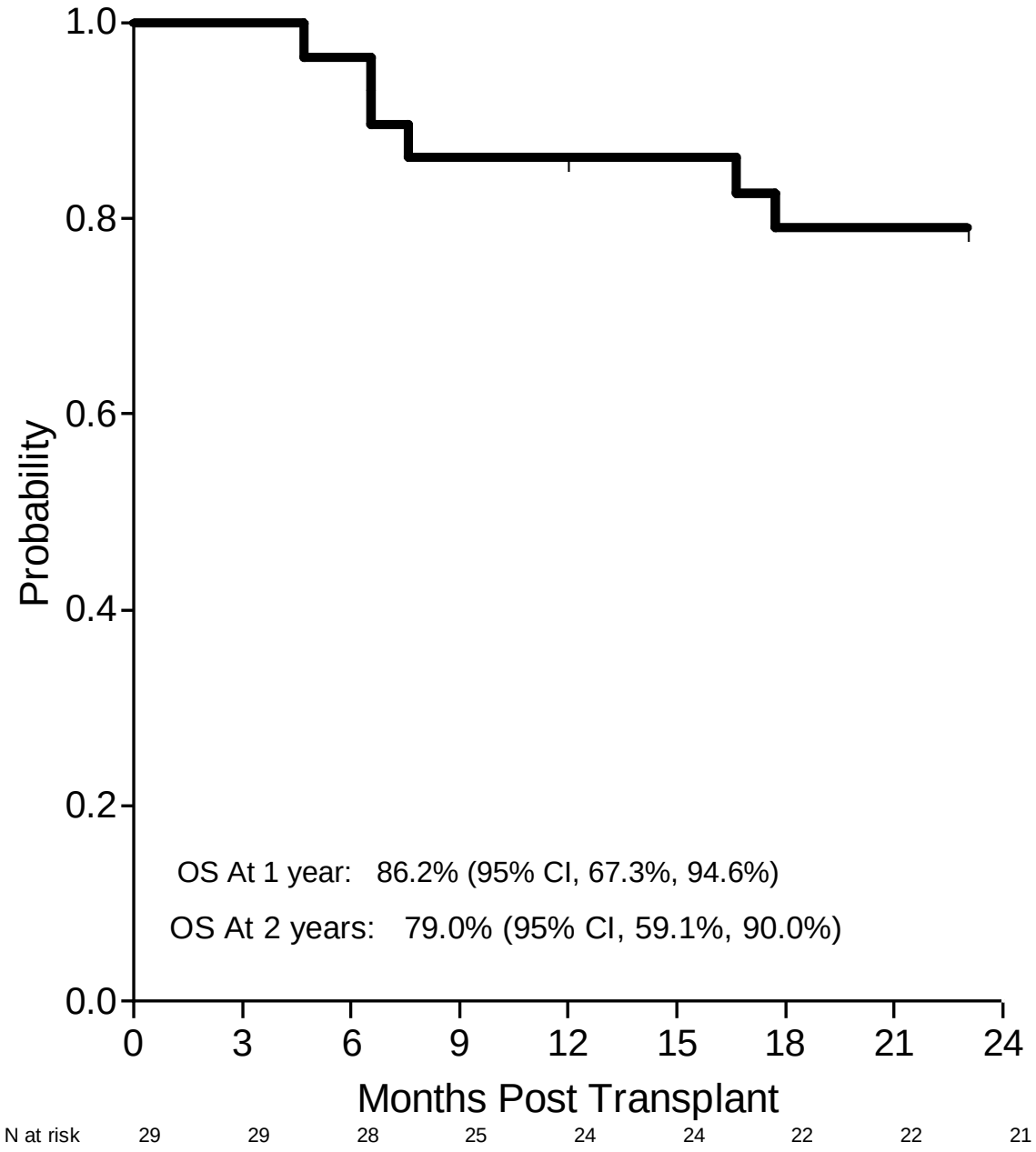


Figure 2A: 100-Day Probability of Acute Grade II-IV Graft-Versus-Host Disease

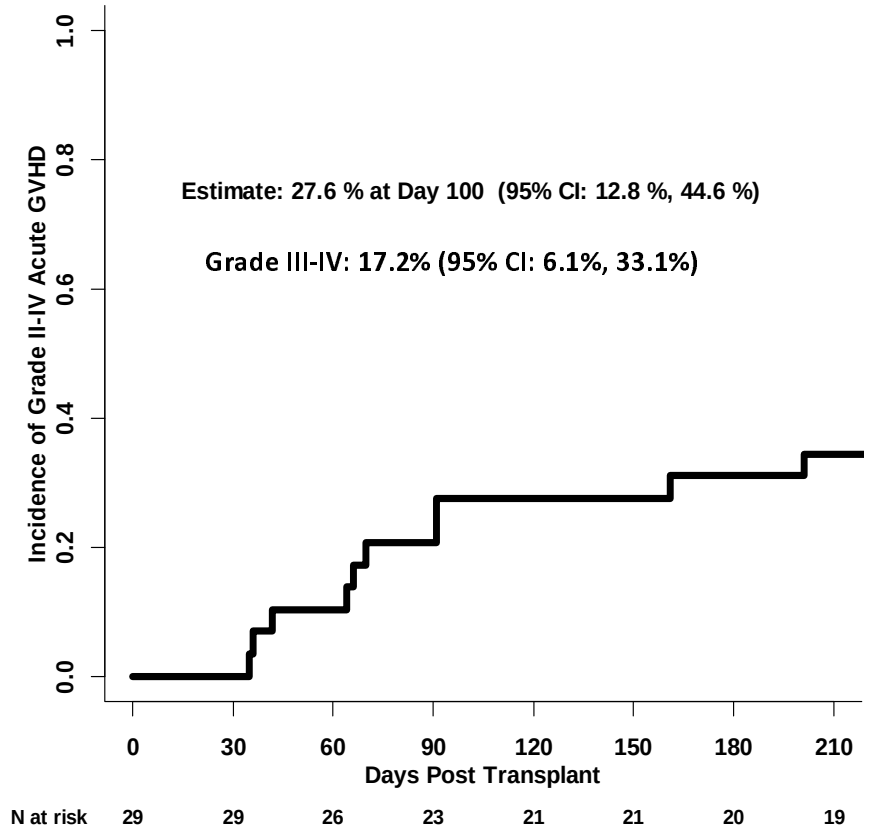
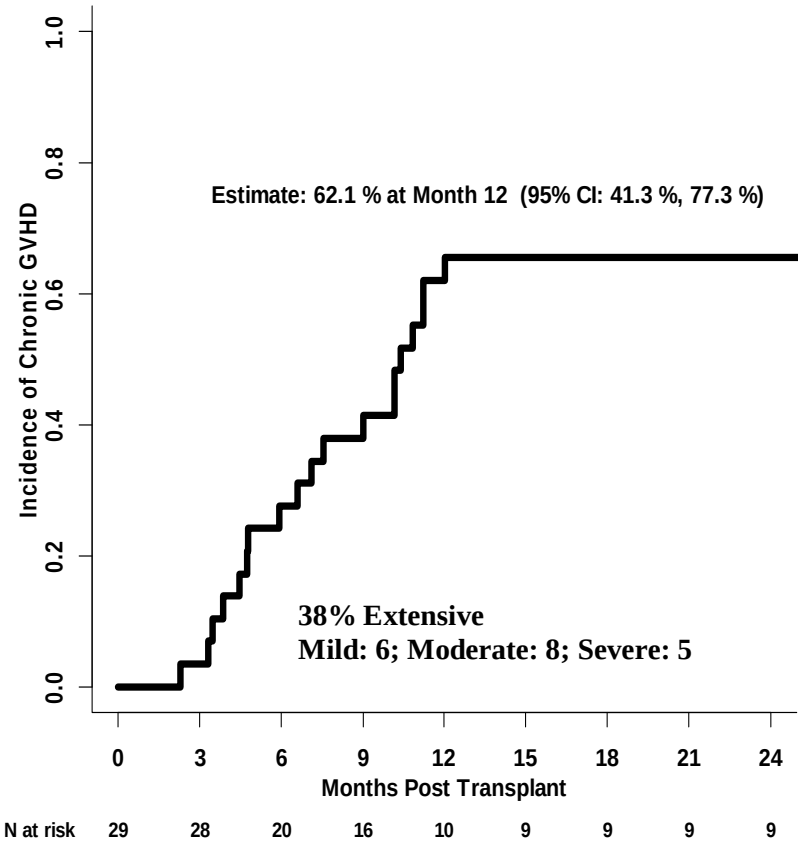


Figure 2B: One-year Probability of Chronic Graft-Versus-Host Disease



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A BMT CTN phase II trial of unrelated donor marrow transplantation for children with severe sickle cell disease

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