A Multicenter Retrospective Analysis Stressing Importance of Long-term Follow-up After Hematopoietic Cell Transplantation for β-thalassemia

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Highlights

- Transplantation for β-thalassemia has a high cure rate and low mortality
- Mixed chimerism is common and needs uniform follow up
- Organ toxicity and growth impairment is higher in transplants ≥7 years of age
- Need for simple measures to uniformly track long-term outcomes and organ functions

Abstract: Allogeneic hematopoietic cell transplantation (HCT) is curative in patients with β-thalassemia major. However, the majority of reports on HCT outcomes lack long-term follow-up data with the exception of single center reports. An international multicenter retrospective data collection and analysis was conducted in 176 β-Thalassemia patients who were 1 year or beyond after first HCT to evaluate follow up methods and outcomes at 7 centers- Median age at HCT was 5.5 years (range, 0.6-18.5) and median follow-up was 7 years (range, 1-20). HCT was predominantly from HLA-matched related donors (91%) with bone marrow as stem cell source (91%) and myeloablative conditioning regimens (88%). Late mortality or persistent chronic graft versus host disease (GVHD) were rare (<2%). Graft rejection was reported in 23% (24% of these occurred beyond 1 year) post-HCT. Of 119 patients with donor chimerism results available for ≥4yrs post HCT, 50% had >95%, 22% had 50-95%, 7% had 20-50% and 25 (21%) had <20% donor chimerism. Organ dysfunction was identified in 10% pre-HCT and in 20% post-HCT even without complete clinical details on all patients. Hypogonadism and elevated
creatinine for age were most commonly reported and significantly higher in recipients ≥ 7 years at the time of HCT (p=0.007), and in those with pre-existing morbidity before HCT (p=0.02). Outcomes were unaffected by pre-HCT ferritin or GVHD. Mean z-scores for height and weight were low at baseline and remained low post-HCT (79%), confirming that growth impairment from disease lacked recovery post-HCT during this follow-up period.

Conclusion: HCT for β-thalassemia has a high rate of cure and low mortality especially in the young, and from HLA-matched related donors. Half the number of recipients live with mixed chimerism that requires continued follow-up due to a risk of late graft rejection (14%). Organ function following HCT when <7 years of age was generally preserved. Hypogonadism, renal dysfunction and growth impairment that failed to correct were late complications identified most frequently in older transplant recipients. Systematic follow-up of individual organs such as lung and heart were inadequate but important. These data support the development of simple measures of uniformly tracking long-term HCT outcomes and organ functions in children and adolescents who undergo HCT for thalassemia, allowing for systematic identification and implementation of standardized surveillance strategies and interventions.

Introduction

β-thalassemia major is a genetic disorder characterized by little or absent β-globin production, hemolysis from resulting unstable α-globin tetramers, ineffective erythropoiesis, and severe anemia that is fatal in the absence of life-long red cell transfusions\(^1\). First reported approximately 3 decades ago, allogeneic hematopoietic cell transplantation (HCT) remains the only widely available curative option for β-thalassemia\(^2\). In the absence of curative therapy, anemia and transfusion-related iron accumulation over time contribute to end organ damage, morbidity and mortality in patients often despite iron chelation. Based on these observations, the Pesaro group identified risk groups in children under 16 years, and stratified HCT outcomes using hepatomegaly, liver fibrosis, and inadequate iron chelation as risk factors for mortality\(^3\).

More recently, improvement in the knowledge of iron pathophysiology has implicated tissue reactive iron species in organ toxicity supported by environmental factors such as infections, supporting continued chelation of toxic iron before and after HCT for best results\(^4\). HCT has been increasingly applied worldwide achieving thalassemia-free
survival rates of 62-84%; survival has improved with time and modern interventions\textsuperscript{5-11}. Other than the risk score, extensive experience with transplant has revealed additional prognostic factors that affect outcomes such as advancing age in childhood, and hepatomegaly\textsuperscript{12-14}.

Outcomes of HCT for β-thalassemia generally report on survival. However, late follow-up and long-term effects after HCT are scarce and limited to single centers and focused organs\textsuperscript{15-21}. This international report on long-term follow-up after HCT for β-thalassemia was undertaken to evaluate late follow-up efforts and outcomes in patients surviving beyond 1-year post-HCT and compiles data obtained from 7 contributing centers.

**Patients, Material and Methods**

De-identified data describing outcomes of children with β-thalassemia surviving \geq 1 year post-HCT were collected from HCT centers in the United States- Chicago, Atlanta, NY, San Francisco and North Carolina (5) and internationally- UAE, Canada(2) following approval from respective Institutional Review Boards using a common case report form. Data from completed forms was collated for this report. Outcomes of interest included engraftment, chimerism studies, graft rejection, graft versus host disease (GVHD), ferritin, growth velocity (z scores) and measures of organ function.

**Endpoints**

The primary outcome was overall survival beyond 1-year post-HCT. Death from any cause after 1 year was considered an event and surviving patients were censored at
last contact. Only graft rejection was reported from all time-points post-HCT due to relevance to outcomes. Primary (early) graft rejection was defined as failure to obtain neutrophil engraftment by day 42 or ANC <0.5 \times 10^9/L, re-transplantation within 42 days of first transplant, donor chimerism <10%, or resumption of regular red cell transfusions. Secondary (late) graft rejection was defined as occurrence of these events after initial hematopoietic recovery\textsuperscript{17}.

The presence of GVHD beyond one year was described according to National Institute of Health criteria and symptoms\textsuperscript{22,23}. Impaired organ function included low left ventricular ejection fraction by echocardiogram (heart) compared to normal for age, low pulmonary function tests (FEV1<80% or adjusted DLCO <60%), impaired renal function defined as proteinuria / elevated serum creatinine for age, and osteoporosis if detected by Dual Energy X-Ray Absorptiometry (DEXA) scan or by susceptibility to fractures. Additional organ dysfunction of medical concern was to be reported if present, and included abnormal hepatic function, visual or auditory impairment. Endocrine function assessment included levels of thyroid (free T4, TSH) and gonadal (FSH, LH, and testosterone in children >10 years of age) hormones. Height and weight were plotted as z scores to eliminate variability of age and gender. Iron accumulation was evaluated by serum ferritin, liver biopsy, or MRI criteria\textsuperscript{24}. Details on post-HCT malignant disorders were requested if diagnosed. Data was collated from the pre-HCT and most recent follow-up visit report beyond the first year after HCT for each patient.

\textbf{Statistical analysis}
The probability of overall survival (OS), disease free survival (DFS), Event (Graft failure/death) free survival (EFS) and was calculated using the Kaplan-Meier estimator from time 0. Time zero (study entry) was 1-year from first transplant as only those who survived beyond the first year were included in the analysis. The incidence of late effects was calculated using the cumulative incidence estimator with death as the competing risk. Chi-square test of independence or Fisher’s exact test was used for categorical covariates; two-sample t-test was used for continuous covariates when comparing groups. Variables tested included: age (<7 and ≥ 7 years, <10 versus ≥ 10 years), pre-HCT ferritin (<1500 and ≥1500 ng/ml, <2000 versus ≥2000 ng/ml), presence of pre-HCT organ dysfunction, and occurrence of acute GVHD in the first year post-HCT. Chronic GVHD was extremely rare and hence not included.

Results

Patient, Disease and Transplant Characteristics

Table I shows characteristics of patients and transplantation. The median age at HCT was 5.5 years (range 0.6-18.5y). All patients were erythrocyte transfusion dependent prior to HCT; 87% were documented to have received regular chelation; Nine (5%) had no chelation and 14 (8%) had no chelation data available. Despite chelation in the majority of patients, the median pre-HCT ferritin was 1638 ng/ml (range, 152-5001), and iron content calculated from MRI or biopsy was 4.1 mg/g dry weight or 6.5 mg/g dry weight respectively. Pre-HCT organ dysfunction was documented in 18 (10%) patients. Pre HCT z scores for height and weight were lower than average for age in 75%, and was -1.2 (20th percentile). Data on cytomegalovirus (CMV) serostatus, performance
scores, measurement of hepatomegaly, and quantitation of erythrocyte transfusions pre-HCT were not available for the majority as they had never been documented systematically.

The majority of patients (91%) received bone marrow grafts from Human Leukocyte Antigen (HLA) matched siblings. Myeloablatative doses of busulfan with cyclophosphamide and cyclosporine were the most common preparative and GVHD regimens used, respectively (88%). Almost all patients (96%) received transplants from a HLA-matched familial donor.

**Overall Survival:**
Median follow up was 7 years (range, 1-20). The 5, 10 and 15-year probabilities of overall survival were 98% (CI 0.92-0.99) (Figure 1). Only three deaths were reported beyond the first year post-HCT- two were from complications of chronic GVHD and one due to fungal infection following a failed second transplant performed for graft rejection. Disease free survival was 95% (CI 0.88-0.99), 82% (CI 0.64-0.91) and 75% (CI 0.52-0.87) at 5, 10, and 15 years post-transplant respectively in patients.

**Graft versus host disease:**
Of 176 children, 46 (27%) had developed acute GVHD in the first year. Acute GVHD rates were higher with stem cell sources other than bone marrow (24% versus 57%; p=0.01) but was unaffected by conditioning regimen, age, and pre-HCT ferritin levels. Only three patients were reported to have chronic GVHD (<1%), all scored as extensive,
and all in children >7 years of age. At study entry (1-year post-HCT), 92% had discontinued systemic immunosuppression.

**Engraftment and graft rejection**

Graft failure free survival was 77% (CI 0.62- 0.81) at 5, 10, and 15 years post-transplant. (Figure 1). Primary graft rejection was described in 15 children and secondary graft rejection in 25, thus resulting in an overall graft rejection rate of 23%. The majority of secondary graft rejections (n=19; 76%) occurred within the first year. Six patients (24%) lost their grafts beyond 1-year post-HCT. Graft rejection rate was higher in young patients (<7yrs) compared to the older subgroup but the difference was not statistically significant (26% versus 15% respectively, p=0.08). There was no correlation with conditioning regimen or use of ATG, but the number that had these variables were small. Seventeen patients (43%) underwent a second HCT, all but one from the same donor, and 12 (71%) of these received TBI based regimens for the second HCT. One death from fungal infection was reported in this group. Extensive details following second transplants were not collected. However, at least three patients had graft rejection following second transplants.

**Donor Chimerism**

Donor chimerism was available in 119 patients at or beyond four years following HCT. Of these, 59 (50%) had >95%; 27 (23%) were between 50-95%; eight (7%) had intermediate levels between 20-50% and 25 (21%) had very low levels at <20% donor chimerism. When data at multiple time points was available (n=59), the majority (n=54)
maintained stable donor derived engraftment, however, two patients exhibited a declining trend. In these two patients, donor chimerism decreased from 75-95% at 1 year to 50-75% at or after 2 years. The interval between declining donor chimerism and resumption of red cell transfusion therapy was not available on all patients with graft tr. Eight patients received second transplants for low donor chimerism associated with disease recurrence.

**Growth**

Height and weight data when available pre-HCT and converted to z scores, were lower in the majority (75%) compared to the normal population, with a median score of -1.2 (at the 20% percentile). Baseline pre-HCT z scores for height and weight were significantly lower in those ≥7 years of age compared to those in younger patients (p=0.003 and 0.014 respectively). Low z-scores for height and weight persisted at 1, 2, and ≥4 years post-HCT demonstrating an absence of catch-up growth (Table II). However, there was no correlation noted between growth patterns, transplant associated complications and iron overload.

**Endocrine function**

Thyroid studies were available pre-HCT in 85 patients and were abnormal in 17 – (20%). No new abnormalities were reported post-HCT (n=76) (Table III). Gonadal dysfunction, reported as an abnormal FSH, LH or testosterone in eligible pre-pubertal and pubertal patients was identified in 5/18 (19%) patients pre-HCT and 18/49 (37%) post-HCT. No center tracked or reported pregnancy or infertility.
**Organ function**

Pulmonary, cardiac, and renal functions were reported as abnormal for age in 4/18 (22%), 2/133 (<1%), and 1/136 (<1%) patients pre-HCT, respectively. After HCT, renal functions (identified by an abnormal serum creatinine level for age) were reported in 10/51 (20%) patients with no documented treatment modifications reported based on the level of dysfunction. No cardiac function abnormalities were reported following HCT. Impaired pulmonary function was reported in 4/21 (19%). Vision and hearing abnormalities were reported in only 2/163 (1%). Skeletal abnormalities with fractures or an abnormal DEXA scan were reported in 3/169 patients (1 with multiple fractures, 2 with abnormal DEXA scans). No malignant disorders were reported post-HCT. Overall, organ involvement and/or endocrine dysfunction was present in 30 recipients (four had multiple impairments). Organ or endocrine impairment did not correlate with pre-HCT ferritin, acute GVHD, donor source, or conditioning regimen (Table IV). However, impaired function was more prevalent in the presence of pre-existing organ dysfunction (61 % vs 39%; p=0.01) and in older patients who were ≥ 7y at the time of HCT (12 vs 28%; p=0.008).

**Iron burden**

All patients with β-thalassemia have a positive iron balance from erythrocyte transfusions as described in Table I. Assessment of iron by MRI of the liver was available in 15 children post-HCT. An abnormal R2 and liver iron overload was present
in 33% (n=5). Cardiac T2* abnormalities were reported in 25% (n=4/20). Of note, iron overload was similarly documented ≥ 4 years post HCT.

Serum ferritin levels were high pre-HCT in the majority of patients. The median level was 1638 ng/ml (range, 152-5001) in 75% despite regular chelation in all reported cases (87%). Ferritin levels continued to remain elevated with a median of 1845 ng/ml (range, 154-5512) at 1 year post-HCT and 2367 ng/ml (range, 179-9900) at 2 years post-HCT respectively. Only ≥ 4 years did ferritin levels begin to trend downward with a median 870 ng/ml (range, 52-6847). Pre HCT iron levels did not adversely impact HCT outcomes or organ functions significantly (Table IV). Specific data on adequacy, type or duration of chelation was beyond the scope of this analysis.

**Quality of Life (QOL) evaluation**

QOL was tracked sparsely at all centers. Sixteen patients had completed QOL questionnaires post-HCT. QOL efforts may have focused on patients reporting problems. Physical, emotional, social or school related difficulties were reported post-HCT in 6, 7, 4 and 2 of the 16 patients respectively. The small numbers precluded correlation with age, and other variables, but indicate the prevalence of complications and the need for systematic tracking especially between varying transplant methods.

**Discussion**

We report on long-term follow up and late complications noted after allogeneic HCT for β-thalassemia major in childhood as reported from 7 institutions across 2 continents in
patients who survived 1 year and beyond post-HCT and hence were evaluable for late
effects. The majority underwent matched related donor HCT, considered the lowest risk
with best outcomes. Compared with previous studies, this report presents the largest
collection of long-term follow-up data from multiple centers, on young transplant
recipients at a diverse group of transplant centers. Patients were treated with similar
conditioning regimens and donor sources, and followed beyond the risk period for acute
post-transplant complications\textsuperscript{13,14}. To our knowledge, this is the first such report on HCT
survivors of beta thalassemia from multiple international institutions.

β-thalassemia patients were able to lead disease-free functional lives with low risk of
late mortality after related donor transplants. Long-term survival beyond 1 year was
excellent compared to other reports, likely due to young recipient age and the ideal
donor source\textsuperscript{26-28}. Though there was no coordinated prospective comprehensive long-
term follow-up within this group, late complications were still identified in 20% of
patients, and we would infer, under-reported. The spectrum of late effects included renal
function impairment, altered lung function, bone health impairment and vision and
hearing abnormalities, with some abnormalities documented on pre-HCT evaluations.
Complications were similar to those described in HCT survivors of malignant and
nonmalignant disorders\textsuperscript{29-33}. Since this was a cross-sectional review at a single time-
point post-HCT, the prevalence and cumulative incidence of late effects such as
malignant disorders may not be fully evident and may manifest over time, especially
when HCT is performed at a young age. It is crucial that these measures be tracked
over time in future studies.
In this young demographic, the impact of growth is important. Although it is believed that in the era of optimal transfusion and adequate iron chelation therapy- the majority of transplants were performed after the year 2000- growth and pubertal development would be preserved, pre-HCT growth scores were significantly lower than the normal population\textsuperscript{34,35}. HCT failed to positively impact growth velocity post-HCT. While there may be a contribution from high dose chemotherapy based myeloablative conditioning regimens, it is likely that disease and pre-HCT transfusion burden contributes to this lack of recovery. In addition, the pre HCT height and weight scores were lower in the older (≥7 yr. cohort) suggesting the cumulative impact of disease on growth, and the time lag to catch up.

Hypogonadotropic hypogonadism and abnormal renal function were the most common late effects described. The incidence of hypothyroidism was lower than that previously described\textsuperscript{30,31}. Fertility or pregnancy was not reported in any patient but may have been due to the young age at follow up. The pre-HCT therapy such as red cell transfusions, iron accumulation and chelation therapy contribute to the development of post-HCT complications as noted by the number of patients that had organ function impairment during pre-HCT work up. Transplant preparative regimens such as myeloablative doses of busulfan can add to the development of late complications such as gonadotoxicity. However, busulfan is usually associated with primary gonadal failure\textsuperscript{36-38}. The hypogonadotrophic gonadal failure also noted in this group of patients post-HCT is likely due to iron deposition and damage to the pituitary in addition to busulfan toxicity\textsuperscript{39}. 
Late complications were seen more frequently in those with pre-HCT organ function impairment and older age (≥7yrs) at transplant (Table IV). There was no effect of acute or chronic GVHD, donor type, and conditioning regimen on late complications, but the majority of patients received similar myeloablative conditioning regimens and marrow from matched sibling donors with low rates of GVHD, making comparison with other variables unreliable. These factors influence mortality rates early (in the first year) after HCT. Late complications will be influenced by disease burden. Our findings confirm that the age threshold of 7 years previously reported in analyses of early outcomes for β-thalassemia are also important for the development of late effects of HCT. We were unable to analyze patients >14 years of age (described as a high risk group) as a separate group due to the small number of older patients\textsuperscript{13}. The impact of age on transplant outcomes even in the era of adequate oral chelation therapy supports the argument that β-thalassemia is a progressive disease. The resulting tissue damage and morbidity from iron exposure starts early, during childhood.

Fifty percent of patients had full donor chimerism. However, unexpectedly, many patients had mixed chimerism despite the predominant use of myeloablative regimens. Mixed chimerism in non-malignant disorders is often associated with reduced intensity transplants\textsuperscript{9,40-42}. This pattern of mixed chimerism is prevalent in thalassemia and may be due to engraftment barriers posed by transfusion exposure, alloreactive antibodies, and recipient immunocompetence\textsuperscript{17,43,44}. However, as previously reported, most patients maintained stable mixed chimerism long-term post-HCT\textsuperscript{45}. Since serial early
engraftment data before day 100 was not available, we were unable to correlate early engraftment patterns with late chimerism and predictability of graft rejection. Graft rejection was highest in the first year post transplant (23%). However, late graft rejection, though uncommon, was described as a complication in a small group contrary to previous reports. Graft rejection did not seem to be influenced by host immunodepletion (ATG), disease class and chelation, use of specific conditioning agents, or mixed chimerism on day +100. Some patients went on to successful second transplants from the same donors.

When interpreting the results of our analyses, we recognize that there are limitations such as the lack of uniformity and detail to the follow up process in many patients. Factors responsible include lack of adoption of uniform follow-up guidelines, poor patient and provider compliance, payor non-compliance, and migration of care to the non-transplant arena. We draw attention to these obstacles with this report and seek to increase awareness regarding long-term follow up. Our follow up period is likely too short to detect additional late complications such as new malignancies. Important aspects of well-being such as a formal assessment of quality of life and health care utilization are also currently lost during follow up. The limitations noted in this report which tracks a large cohort of HCT survivors provides insight into both results and obstacles to health-related follow-up after HCT for β-thalassemia. Our intention with this report is to highlight the importance of uniform, careful, and systematic follow up to better serve these patients.
Conclusions

In summary, this report suggests that HCT survivors of thalassemia are generally in good health and have low rates of late mortality. However, even without uniform prospective follow-up, late effects were reported in 20% of children post-HCT and affected gonads, kidneys and functional status. Organ toxicity and growth impairment was higher in those that received transplants $\geq 7$ years of age. Surprisingly, complications noted in the long-term were unaffected by pre-HCT ferritin or HCT related factors such as acute GVHD, and donor source. These findings of late effects support the need to develop standardized simple formats for uniform post-HCT follow up across geographical regions to understand the risk and nature of late effects over time, promote newer methods of HCT that can achieve engraftment and reduce adverse late effects, and to provide timely diagnosis and intervention to those who develop such toxicities. We highlight with this report the need for development of consensus based prospective medical surveillance guidelines and long-term follow-up registries for HCT patients with individual non-malignant disorders and recognize the responsibility of providers and healthcare insurance agencies in tracking post-HCT health.
References:


Figure 1 legend: Overall survival and event (graft failure)-free survival following hematopoietic stem cell transplantation in children ≥1-year from transplant for β thalassemia major

Footnote: OS = Overall Survival; EFS = Event Free Survival; Cum=cumulative
Table I. Patient and transplant characteristics

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>N (%) or median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>176</td>
</tr>
<tr>
<td>Age at HCT, years</td>
<td>5.5y (range 0.6-18.5y)</td>
</tr>
<tr>
<td>&lt;7y</td>
<td>114 (80%)</td>
</tr>
<tr>
<td>&gt;7y</td>
<td>62 (20%)</td>
</tr>
<tr>
<td>Male</td>
<td>81 (47%)</td>
</tr>
<tr>
<td>HCT at non US centers</td>
<td>135 (77%)</td>
</tr>
<tr>
<td>Pre Transplant iron status</td>
<td></td>
</tr>
<tr>
<td>Ferritin— Abnormal &gt;1000ug/l</td>
<td>92/122 (75%), Median 1638 ng/ml (range 157-5512)</td>
</tr>
<tr>
<td>Liver MRI - Abnormal (Iron &gt;3mg/g dry weight)</td>
<td>11/12 - 4.1 mg/g dry weight (range 1.5-12)</td>
</tr>
<tr>
<td>Liver biopsy</td>
<td>14/14 - Iron overload, Fibrosis-3, median iron 6.5 mg/g dry weight (range 2-22)</td>
</tr>
<tr>
<td>Cardiac MRI - Abnormal T2* &lt;20</td>
<td>1/9 - Median T2* 29.7msec (range 9.9-39)</td>
</tr>
<tr>
<td>Conditioning regimen - Myeloablative</td>
<td></td>
</tr>
<tr>
<td>Busulfan + cyclophosphamide</td>
<td>155 (88%)</td>
</tr>
<tr>
<td>Missing</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>T cell serotherapy - ATG</td>
<td></td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>14 (8%)</td>
</tr>
<tr>
<td>Unknown/None</td>
<td>68 (39%)</td>
</tr>
<tr>
<td>GVHD prophylaxis - CSA based</td>
<td></td>
</tr>
<tr>
<td>Tacrolimus based</td>
<td>14 (8%)</td>
</tr>
<tr>
<td>Missing</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Donor HLA matching - HLA Matched related donor</td>
<td></td>
</tr>
<tr>
<td>HLA Matched unrelated donor</td>
<td>161 (91%)</td>
</tr>
<tr>
<td>HLA mismatched donor</td>
<td>6 (4%)</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Donor cell source</th>
<th>Bone Marrow</th>
<th>Peripheral blood</th>
<th>Umbilical Cord Blood (UCB)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>162 (+ UCB 2) (92%)</td>
<td>3 (2%)</td>
<td>11 (6%)</td>
</tr>
</tbody>
</table>

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<tbody>
<tr>
<td></td>
<td>24 (14%)</td>
<td>39 (22%)</td>
<td>61 (35%)</td>
<td>51 (29%)</td>
<td>1 (&lt;1%)</td>
</tr>
</tbody>
</table>

| Median follow-up of survivors, years | 7 y (range 1-20) |

* Only pre-pubertal / pubertal patients eligible for testing for gonadotoxicity

### Table II: Growth parameters presented as z-scores for height and weight

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>Pre HCT</th>
<th>1 year post HCT</th>
<th>2 years post HCT</th>
<th>≥4 years post HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean z-scores for height (range)</td>
<td>-1.2 (-6 to +1.8)</td>
<td>-1.3 (-4.3 to +1.8)</td>
<td>-1.4 (-4.1 to +2.7)</td>
<td>-1.3 (-2.7 to +1.9)</td>
</tr>
<tr>
<td>Mean z-scores for weight (range)</td>
<td>-1.17 (-8 to +1.8)</td>
<td>-1.5 (-4.7 to +1.5)</td>
<td>-1.3 (-5.2 to +2.8)</td>
<td>-1.3 (-4.9 to +2.2)</td>
</tr>
</tbody>
</table>

HCT = hematopoietic cell transplant
Table III: Incidence of impaired end organ function before and after transplant

<table>
<thead>
<tr>
<th>END ORGAN FUNCTION</th>
<th>ABNORMAL PRE HCT (Number/Total tested)</th>
<th>ABNORMAL POST HCT (N/Total tested)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary function</td>
<td>4/18 (22.2%)</td>
<td>4/21 (19%)</td>
</tr>
<tr>
<td>Cardiac function</td>
<td>2/133 (1.5%)</td>
<td>0/64</td>
</tr>
<tr>
<td>Renal function</td>
<td>1/136 (0.7%)</td>
<td>10/51 (19.6%)</td>
</tr>
<tr>
<td>Gonadotoxicity*</td>
<td>5/18 (27.78%)</td>
<td>18/49 (36.7%)</td>
</tr>
<tr>
<td>Thyroid function</td>
<td>17/86 (19.7%)</td>
<td>0/76</td>
</tr>
<tr>
<td>Vision</td>
<td>2/154 (1.2%)</td>
<td>2/163 (1.2%)</td>
</tr>
<tr>
<td>Hearing</td>
<td>2/154 (1.2%)</td>
<td>2/163 (1.2%)</td>
</tr>
<tr>
<td>Skeletal involvement</td>
<td>0/154</td>
<td>3/169 (1.7%)</td>
</tr>
<tr>
<td>Post-HCT malignancy</td>
<td>0/136</td>
<td>0/163</td>
</tr>
</tbody>
</table>

* Numbers limited by patient age
HCT- Hematopoietic stem cell transplantation
Table IV. Significance of transplant variables on late post-transplant outcomes

<table>
<thead>
<tr>
<th>Variable*</th>
<th>Graft rejection</th>
<th>Mixed chimerism (≥4 years post-HCT)</th>
<th>Post-HCT organ dysfunction</th>
<th>Z score height (pre-HCT)</th>
<th>Z score weight (pre-HCT)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age cut-off of 7 years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7 years (N=77)</td>
<td>P=0.08</td>
<td>P=0.68</td>
<td>P=0.0008</td>
<td>P=0.003</td>
<td>P=0.014</td>
</tr>
<tr>
<td>≥7 years (N=42)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Donor source</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Marrow (N=110)</td>
<td>P=0.73</td>
<td>P=0.03</td>
<td>P=0.22</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Other (N=19)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Acute GVHD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (N=126)</td>
<td>P=0.32</td>
<td>P=0.48</td>
<td>P=0.12</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Yes (N=46)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Pre-HCT ferritin level</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&lt;1500 ng/ml (N=53)</td>
<td>P=0.07</td>
<td>P=0.82</td>
<td>P=0.39</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>&gt;1500 ng/ml (N=69)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-HCT organ dysfunction (N=30)</td>
<td>P=0.3</td>
<td>P=0.9</td>
<td>P=0.01</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

N=number; HCT = hematopoietic stem cell transplant

*Additional variables that were tested but were not significant included ferritin <2000, donor conditioning and center. Age <10 showed similar result for z score.
Figure 1

Survival Functions

Cum Survival

Years

OS

EFS

0.0  0.2  0.4  0.6  0.8  1.0

0.0  5.0  10.0  15.0  20.0  25.0