Enzyme Replacement is Associated with Better Cognitive Outcomes after Transplant in Hurler Syndrome

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Objective To investigate whether intravenous enzyme replacement therapy (ERT) benefits cognitive function in patients with mucopolysaccharidosis type IH (Hurler syndrome) undergoing hematopoietic cell transplantation (HCT).

Study design Data were obtained for 9 children treated with HCT + ERT (ERT group) and 10 children treated with HCT only (no-ERT group) from neuropsychologic evaluations before HCT and at 1-year and 2-year post-HCT follow-up.

Results At 2 years after HCT, children in the ERT group lost 9.19 fewer IQ points per year compared with children in the no-ERT group ($P = .031$). Furthermore, the ERT group improved in nonverbal problem solving and processing, whereas the no-ERT group declined, resulting in a difference of 9.44 points per year between the 2 groups ($P < .001$).

Conclusion ERT in association with HCT enhances cognitive outcomes, providing new evidence that ERT is a valuable addition to the standard transplantation protocol. Although the mechanism responsible for this improved outcome is unknown, both direct benefits and indirect effects must be considered. *(J Pediatr 2013;162:375-80)*.

Mucopolysaccharidosis (MPS) type I is a lysosomal storage disease characterized by a deficiency in the enzyme α-L-iduronidase with consequent progressive accumulation of glycosaminoglycans in nearly all organ systems, leading to a myriad of complications, including ophthalmologic, airway, pulmonary, cardiac, and orthopedic problems. MPS type IH (Hurler syndrome), the most severe form, is fatal if untreated within the first decade of life. MPS IH has central nervous system (CNS) involvement in early childhood, resulting in cognitive deterioration.[1]

Enzyme replacement therapy (ERT) alone is used to treat less severe forms of MPS I, because intravenous (IV) enzyme is thought to be ineffective in treating cognitive decline. Hematopoietic cell transplantation (HCT) is the standard of care for patients with MPS IH to treat CNS disease. HCT appears to provide enzymes to the CNS and arrest neurologic deterioration, likely by engraftment of donor-derived macrophages and microglia within the brain parenchyma.[2]

HCT should be performed early in life (within the first 2 years) before irreversible damage occurs. As part of the preparative conditioning for HCT, busulfan, known to be neurotoxic, eliminates existing marrow to make way for donor cells. Monitoring of busulfan is now the standard of care to limit excessive toxicity by determining metabolism of the first dose and adjusting all subsequent doses based on patient-specific pharmacodynamics.[2] Careful dosing and monitoring can decrease the neurotoxic effects of busulfan.[3] Although HCT slows or halts progression of cognitive decline, even with improved treatment approaches many children with MPS IH continue to show cognitive and physical impairments.[4,5] ERT delivered intravenously in combination with HCT decreases morbidity and mortality.[6-8] It is not a universal treatment approach, however[9]; some have argued that ERT provides no benefit in a healthy child with MPS IH and that ERT could alter rates of engraftment.[10] Even though the use of ERT with HCT improves transplantation survival,[6,7] no previous studies have investigated whether combined treatment affects CNS function as measured by neuropsychologic evaluation.

CNS	Central nervous system
CsA	Cyclosporine
ELC	Early Learning Composite
ERT	Enzyme replacement therapy
HCT	Hematopoietic cell transplantation
IV	Intravenous
MPS	Mucopolysaccharidosis

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Methods

The study group included all children with MPS IH treated with HCT at our institution beginning in 2002 (n = 19). The year 2002 was selected because busulfan monitoring was initiated then as part of the treatment protocol, which afforded some control over its neurotoxic effects. Nine of the 19 children received combined HCT + ERT (ERT group) at the University of Minnesota Blood and Marrow Transplant Service and had neuropsychologic evaluations before and at 1 year and 2 years after HCT. All assessments were performed as part of prescribed multidisciplinary clinical protocols. Ten children were treated with HCT only, underwent the same evaluations, and were used for comparison (no-ERT group). Since 2005, all children undergoing HCT have received ERT at this institution. Thus, necessarily the ERT and no-ERT groups were serially recruited for the study, from 2002 to 2005 for the no-ERT group and from 2005 onward for the ERT group. Transplantation preparative regimens have remained relatively unchanged since 2002. Consent was obtained for sharing medical, clinical, and neurobehavioral function data from medical files.

HCT Protocols

For all but 3 of the 19 patients, the HCT protocol included a fully myeloablative protocol including cyclophosphamide (50 mg/kg for 4 daily doses) and IV busulfan (1.1 mg/kg/dose every 6 hours for 16 doses), with the busulfan dose adjusted as necessary to maintain an area under the receiver operating characteristic curve of 900-1500 uM*minute (cumulative dosing). Three patients, all in the no-ERT group, received a reduced-intensity conditioning regimen owing to concerns about increased risk based on pretransplantation assessment.[11] The reduced-intensity regimen consisted of IV busulfan (0.5 mg/kg/dose every 6 hours for 8 doses), fludarabine 35 mg/m^2 daily for 5 doses, and 200 cGy of total body irradiation. Two of the 3 patients received the reduced-intensity regimen because of older age at the time of transplantation (31 and 34 months),[4] and the third did so because of cardiac-related concerns. The latter patient had a low ejection fraction (27%) and required support with digoxin before transplantation. Of these 3 patients, 1 older patient with a sibling donor demonstrated successful engraftment. The other older patient and the patient with cardiac concerns received cord blood grafts and did not achieve engraftment with the reduced-intensity regimen. They subsequently underwent retransplantation with the same regimen using unrelated grafts, and both subsequently achieved engraftment.

Sixteen of the 19 patients (excluding the 3 who received the reduced-intensity regimen) received either antithymocyte globulin (n = 15) or Campath-1H (n = 1) as immunotherapy before transplantation. Graft-versus-host disease prophylaxis included cyclosporine (CsA) in all patients, with mycophenolate mofetil (n = 10) or methylprednisolone (n = 5) for cord blood recipients, and CsA and methotrexate for 2 recipients of related marrow grafts. One patient underwent transplantation with a sibling donor and a reduced-intensity preparative regimen using CsA and mycophenolate mofetil.

ERT Protocol

The patients enrolled on a prospective, Institutional Review Board–approved protocol received weekly ERT comprising 10-14 doses of laronidase, 0.58 mg/kg IV, before HCT and 8 doses after HCT. Posttransplantation doses were designed to provide a source of enzyme until the anticipated time of donor engraftment, as described previously.[7]

Measure of Neurocognitive Development

A standard neuropsychologic evaluation protocol used in all patients evaluated before and after HCT included assessment of cognitive developmental status with the Mullen Scales of Early Learning,[12] normed in the US for children from birth to age 68 months. The Mullen Scales yield an age-based standard score (mean ± SD, 100 ± 15), known as the Early Learning Composite (ELC), reflecting overall cognitive development and is an early estimation of IQ. The ELC represents the aggregate of scores in separate functional domains, including Visual Reception (nonverbal problem solving and processing), Fine Motor (finger/hand strength and dexterity), Receptive Language (listening and understanding what is spoken), and Expressive Language (spoken language proficiency) skills. The Gross Motor domain was not included in this assessment, because it does not contribute to the ELC. Cognitive developmental functioning was assessed at baseline before HCT, as well as at 1 year and 2 years post-HCT.

Treatment-Related Variables

The following treatment-related data were used in adjusted analyses: age at transplantation, baseline ELC, and length of hospital stay in the acute posttransplantation period. We also recorded type of donor (cord blood or sibling), presence of chronic graft-versus-host disease, percent donor engraftment, and posttransplantation enzyme levels.

Analytic Approach

Baseline characteristics with respect to ERT use were tabluated. Unadjusted longitudinal analyses present the average scores for each group at each point over time. Generalized estimating equations[13] were used with an exchangeable working correlation structure to account for correlated observations. Covariates were selected a priori to be potential confounders or independent predictors of outcomes. Robust variance estimation was used for CIs and *P* values. A sensitivity analysis was examined to evaluate the dependence of results on the choice of working correlation structure; use of an independence working structure did not change the results appreciably. All statistical analyses were performed using R version 2.9.2 (R Foundation for Statistical Computing, Vienna, Austria) with the "gee" library version 4.13-14 (http://cran.r-project.org/web/packages/gee/index.html).

Results

Patient characteristics at baseline and during HCT are summarized in Table I. No children in the ERT group died, but in the no-ERT group, 2 of the 10 patients died after transplantation, 1 patient at 104 days due to reactive airway disease and aspiration pneumonia and another patient at 231 days due to refractory autoimmune hemolytic anemia. In both groups, all surviving patients achieved at least 80% donor engraftment by 2 years posttransplantation except 1 patient in the ERT group, who achieved only 47% donor engraftment. In addition, by 2 years posttransplantation, all patients had normal enzyme levels except the patient who achieved 47% engraftment (enzyme levels in the "carrier range"). In an effort to follow an intent-to-treat type of analysis, analyses were evaluated both including and not including the 2 patients who died. When the patients who died were included, their values were set to 0 at the 1-year and 2-year follow-ups.

Unadjusted Analyses

Figure 1 presents trajectories of ELC scores for the ERT group versus the no-ERT group from baseline to 1 year and 2 years post-HCT. Although the ERT group began with lower ELC scores than the no-ERT group, these patients exhibited a less dramatic decline, and at 2 years post-HCT, their ELC scores were higher on average than those of the no-ERT group, regardless of inclusion of deaths. Figure 2 (available at www.jpeds.com) presents trajectories for individuals.

Table I. Patient characteristics

Covariate	Overall (n = 19)	ERT (n = 9)	No-ERT (n = 10)
Male sex, n (%)	11 (57.9)	5 (55.6)	6 (60.0)
Age at HCT, months	17.5 (7.9)	18.0 (6.8)	17.1 (9.1)
Time since evaluation, days	54.6 (72.2)	17.1 (2.2)	88.3 (88.0)
Cord blood donor, n (%)	15 (78.9)	6 (66.7)	9 (90.0)
Sibling donor, n (%)	4 (21.1)	3 (33.3)	1 (10.0)
GVHD prophylaxis, n (%)			
CsA/MMF	10 (52.6)	6 (66.7)	4 (40.0)
CsA/MTX	3 (15.8)	3 (33.3)	0 (0)
MP/CsA	6 (31.6)	0 (0)	6 (60.0)
Ablation, n (%)			
ATG	15 (78.9)	8 (88.9)	7 (70.0)
Campath	1 (5.3)	1 (11.1)	0 (0)
No ATG	3 (15.8)	0 (0.0)	3 (30.0)
No GVHD, n (%)	15 (78.9)	7 (77.8)	8 (80.0)
GVHD grade II, n (%)	3 (15.8)	2 (22.2)	1 (10.0)
GVHD grade IV, n (%)	1 (5.3)	0 (0)	1 (10.0)
Length of hospital stay, days	47.6 (21.8)	46.0 (19.3)	49.5 (25.6)
Baseline scores			
ELC*	87.6 (16.4)	84.0 (15.0)	90.8 (17.7)
Visual Reception T-score†	44.2 (10.9)	40.6 (10.0)	48.4 (10.9)
Fine Motor T-score†	42.8 (10.8)	39.9 (9.8)	46.1 (11.6)
Receptive Language T-score†	39.4 (11.2)	39.7 (9.6)	39.0 (13.4)
Expressive Language T-score†	42.1 (9.8)	40.0 (8.7)	44.5 (10.9)

ATG, antithymocyte globulin; *GVHD*, graft-versus-host disease; *MMF*, mycophenolate mofetil; *MP*, methylprednisolone; *MTX*, methotrexate.
Values presented are mean (SD) or n (%) where indicated.
*Mean, 100 ± 15.
†Mean, 50 ± 10.

Table II (available at www.jpeds.com) presents scores by Mullen Scales by domain. At baseline, the ERT group had scores within the average range in the Visual Reception and Expressive Language domains, but below the average range in the Receptive Language and Fine Motor domains. Likewise, the no-ERT group had scores within the average range in the Visual Reception and Expressive Language domains, and below the average range in the Receptive Language domain. However, the no-ERT group had a better baseline Fine Motor domain score (average range) than the ERT group. At 1 year posttransplantation, both groups had below average overall ELC scores, as well as individual Mullen Scale domain scores. At 2 years posttransplantation, the 2 groups remained below average for overall ELC. They were also below average across the Mullen domains with one exception: the ERT group improved to the average range for the Visual Reception domain. Furthermore, the no-ERT group dropped to the impaired range for the Fine Motor domain. When the patients who died were included in the analyses, all scores dropped even further in the no-ERT group. Thus, the analysis that excludes these patients is likely an overly optimistic representation of the no-ERT group's trajectory, which is still significantly lower than that of the ERT group.

Adjusted Analyses

The rate of decline in ELC scores over 2 years was significantly less in the ERT group compared with the no-ERT group, after adjusting for baseline ELC score (ie, pre-HCT) and length of hospital stay (Table III). Being in the no-ERT group was associated with a loss of 12.84 points per year (95% CI, −20.21 to −5.46; $P < .001$), whereas being in the ERT group was associated with a loss of only 3.64 points per year (95% CI, −7.57 to 0.28; $P = .069$). The difference in rates, calculated based on these estimated rates of decline for the ERT and no-ERT groups, indicated that children in the ERT group lost 9.19 fewer points per year

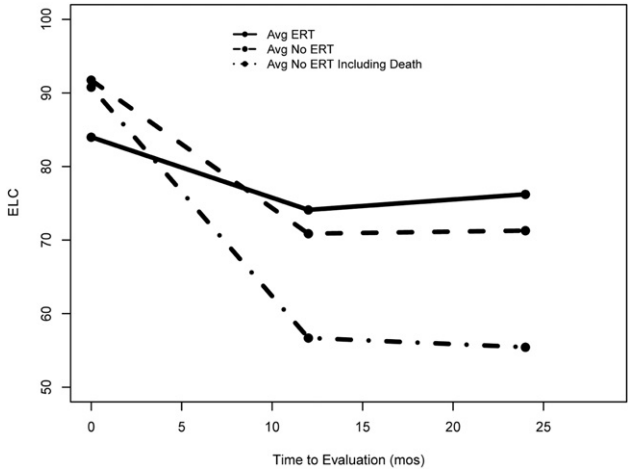

Figure 1. Change in cognitive developmental status after HCT.

Table III. Adjusted analysis results for ELC, first including the 2 deaths (follow-up values at 1 year and 2 years post-HCT imputed as 0) and then excluding the 2 deaths

Covariate	Estimate (95% CI)	*P* value
Baseline ELC	0.78 (0.56 to 0.99)	<.001
Days in hospital	−0.32 (−0.61 to −0.03)	.029
No-ERT (per year)	−12.84 (−20.21 to −5.46)	<.001
ERT (per year)	−3.64 (−7.57 to 0.28)	.069
Difference in rate, ERT versus no-ERT*	9.19 (0.85 to 17.54)	.031
Excluding deaths	**Estimate (95% CI)**	***P* value**
Excluding deaths		
Baseline ELC	0.70 (0.55 to 0.86)	<.001
Days in hospital	−0.06 (−0.16 to 0.03)	.199
No-ERT (per year)	−8.91 (−12.06 to −5.76)	<.001
ERT (per year)	−3.51 (−7.33 to 0.30)	.071
Difference in rate, ERT versus no-ERT*	5.40 (0.50, 10.29)	.031

*Difference calculated based on the estimated rate of each group.

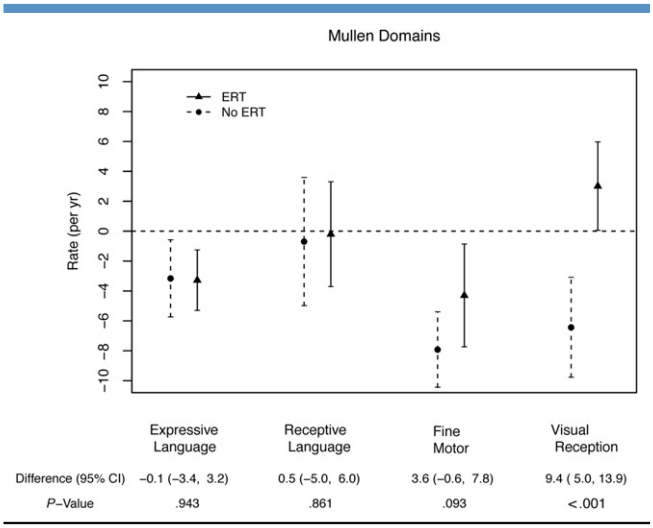

Figure 3. Comparison of domains composing cognitive developmental status 2 years after HCT.

(95% CI, 0.85-17.54; $P = .031$). When the 2 patients in the no-ERT group who died were excluded, this difference was reduced to 5.40 points per year (95% CI, 0.5-10.29), yet remained clinically and statistically significant ($P = .031$).

Given the progressive cognitive deterioration associated with the disease, an additional sensitivity analysis was conducted that also excluded patients who underwent baseline evaluation more than 3.5 months before HCT, owing to the possibility of a decline in ELC in the interval between evaluation and HCT (**Table IV**; available at www.jpeds.com). The difference in the rate of decline between the ERT and no-ERT groups remained significant. Two patients required retransplantation, resulting in a longer time interval between evaluation and HCT. Given possible differential effects on CNS outcomes, the rate of change in ELC was reexamined after excluding these patients; the results remained robust. Results again remained significant after adjustment for use of a reduced-intensity preparative regimen (**Table V**; available at www.jpeds.com). **Figure 3** presents results of the analyses for the 4 Mullen Scale domains that compose the ELC. These analyses adjusted for both baseline score and length of hospital stay and excluded deaths. There was a significant difference in the rate of change for the Visual Reception domain between the ERT and no-ERT groups of 9.44 points per year (95% CI, 4.98-13.90; $P < .001$), nearly a full SD. Furthermore, in this domain the ERT group actually showed a statistically significant improvement over 2 years of 3.01 per year (95% CI, 0.05-5.97; $P = .046$). There were no significant between-group differences in slopes of changes in any of the other domains, although there was a trend toward more favorable outcomes for the ERT group in the Fine Motor domain. An intent-to-treat type of analysis was used to compare results with deaths included and excluded. The analyses including and excluding deaths revealed statistically significant between-group differences, with the ERT group consistently performing better when differences were found.

Discussion

We report an association of short-term cognitive benefits from ERT in patients with MPS IH undergoing transplantation. All patients with MPS IH treated at our institution beginning in 2005 underwent ERT in addition to HCT with the original aim of improving mortality and morbidity.[6-8] An improvement in cognitive functioning was not predicted at the initiation of this protocol.

Our neuropsychologic test results indicated that the children who received the combined ERT + HCT treatment lost fewer ELC points in the 2 years after transplantation compared with the children who underwent HCT without ERT. Given that ELC (equivalent to IQ in older persons) represents an age-based aggregate of diverse abilities (eg, visual, verbal), we were also able for the first time to examine the domains separately to reveal what functional areas may be more or less affected.

The children who received ERT showed significant improvement on the Visual Reception domain, which measures the construct of nonverbal problem solving, not of perception. The improvement in the ERT group contrasts with, and differs significantly from, the no-ERT group's decline in this domain. For the Visual Reception tasks, children are presented with visual information in various forms and patterns, involving localizing, tracking, scanning, matching, and memorizing. Instructions are given verbally and paired with gesture, but speaking is not required for responses. Because it measures nonverbal problem solving skills, the Visual Reception domain is a proxy for nonverbal cognitive ability. Nonverbal problem solving is often used as an estimation of general intellectual ability (eg, the Raven Progressive Matrices test).[14] Improvement in the Visual Reception domain

likely translates to improved nonverbal reasoning. It may reflect the fact that such functions are widely distributed in the CNS, with more than 50% of the human brain dedicated to processing of visual information,[15] and thus with more physical opportunity for benefits from enzyme. An unanswered question is whether certain areas of the CNS are affected differentially.

Why was language unaffected by ERT? Children with MPS disorders have generally been considered to have early language impairment owing to both neurologic impairment and hearing loss (mixed conductive and sensorineural).[16] Language is dependent on environmental input, which is obstructed because of hearing loss. We were unable to control for the effects of environmental variables in this study. Another possibility is that language is intrinsically impaired in MPS disorders early in development, and consequently there is no potential for recovery of function. The development of early language also may be disrupted by the neurotoxic preparative regimen. In longitudinal studies of perinatal focal injury, Stiles[17] noted that language is a system widely distributed in the brain in early development, and that damage in a variety of regions can impede its development. Lateralized specific language systems might not develop normally, because the neural substrate of language has little plasticity.[17] The windows of development of language and visual problem solving have different time courses, and visuospatial cognition may have more potential for recovery. According to Stiles, "the capacity for reorganization and functional compensation is retained" in the case of visual-spatial cognition.[17]

Did hydrocephalus contribute to outcomes? Only 1 child, in the ERT group, had a shunt and was diagnosed with hydrocephalus. The other children in the study, equivalent in both groups, had mildly enlarged ventricles that did not change substantially over time. Was the benefit related to the use of cord blood? There were no statistically significant differences in outcomes between cord blood transplantation and marrow transplantation. Is the benefit due to enzyme crossing the blood-brain barrier? The blood-brain barrier, built of capillary endothelial cells connected with tight junctions,[18] has long been an issue of focus and concern when treating MPS IH with IV ERT, with the enzyme not expected to enter the CNS in clinically beneficial levels.[19,20] The neurologic benefit that recipients of HCT derive from the procedure has been considered a consequence of donor microglial engraftment in the brain with subsequent secretion of iduronidase, and local paracrine cross-correction of the iduronidase-deficient neurons and glia.[21] Irradiation has been shown to enhance donor microglial engraftment in the brain,[22-24] and it is possible that chemotherapy-based regimens also may increase CNS engraftment of donor microglia. In animal models, chemotherapy and radiation have been shown to increase the permeability of the blood-brain barrier,[23] but no conclusive evidence of this has been demonstrated in humans. Thus, it is possible that the administration of IV ERT after transplantation may result in increased penetration of enzyme into the CNS owing to the effect of the transplantation regimen. In addition, in animal models, the blood-brain barrier may be permeable to very high doses of lysosomal enzyme in the peripheral circulation.[25] One hypothesis is that high concentrations of lysosomal enzyme in the blood may engage non–mannose 6 phosphate receptor–mediated transport mechanisms and thus encourage transportation of more enzyme into the CNS in very young patients.

In contrast to this direct effect of donor cells, it has been hypothesized that somatic improvements from IV ERT indirectly support developmental functioning.[26] A healthier child may interact with his environment more actively and experimentally, thus promoting the learning process that underlies development.[27] The trend toward better Fine Motor domain outcomes in the ERT group is consistent with such a theory, given that children use their hands to engage their surroundings and learn.

Accounting for patient deaths complicates this analysis. An intent-to-treat analysis is the well-recognized and accepted standard for randomized clinical trials, but the corresponding analysis here is inhibited by incomplete observations because of deaths. If the deaths were completely independent, then the analysis in which they are excluded entirely would represent an unbiased estimate. However, if missing data due to death are not missing at random, then ignoring them introduces bias and might not represent what would be observed for the group without ERT therapy with no deaths. As such, results are presented both including (assigned a value of 0) and excluding deaths. Both analyses revealed meaningful differences between the 2 treatment groups. Although the appropriate value to assign to patients who die is unclear, we have presented intent-to-treat type results for a plausible choice (value of 0) in an effort better to characterize the potential magnitude of treatment effect.

Despite our small sample size, which is inherent in rare diseases, we find compelling differences between our ERT and no-ERT groups. However, there is always the real possibility that our sample is not representative of MPS IH or its true course after either HCT or HCT + ERT treatment.

The serial recruitment of participants for this study was a limitation. Unknown or subtle differences in multidisciplinary treatment, or even historical factors, might explain between-group differences in response to treatment. Because of our serial recruitment, participant matching across groups was not possible. It is important to note that there was no bias in group selection, given that all participants were included.

Another study limitation is the effect of retransplantation on cognitive outcomes of children in the no-ERT group. Repeated exposure to procedures known to adversely affect the CNS certainly influences cognitive developmental functioning. Moreover, because MPS IH is a progressive disease, the additional time lapse before successful engraftment in these children translated to a delay in the arrest of the disease, likely causing further cognitive decline. Yet excluding these children from the analysis did not change the findings in this study.

This study provides new evidence that ERT is a valuable addition to the standard HCT protocol for MPS IH. It also

raises new questions regarding the permeability of the blood-brain barrier and the effects of high enzyme concentrations in the blood on brain function during the peritransplantation period in children with MPS IH. Given that children with MPS IH who received the combined ERT + HCT treatment remain below average, earlier treatment as a result of newborn screening may point the way to even better developmental outcomes. The findings reported here represent short-term outcomes in the lives of these children. It will be important to continue to follow these children to determine whether differences in cognitive functioning persist in the long term. ■

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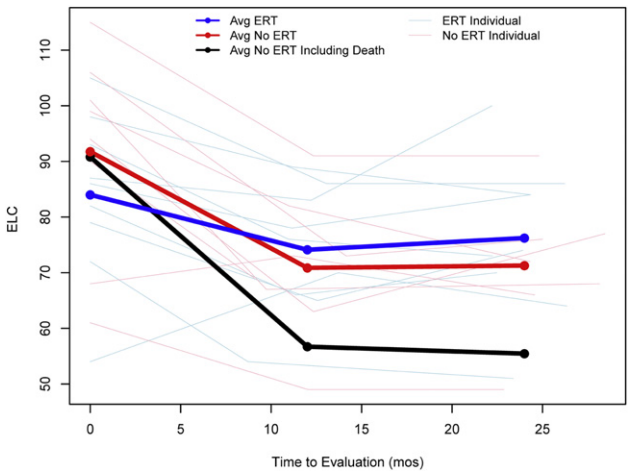

Figure 2. Change in cognitive developmental status after HCT. Individual trajectories are presented with overall group averages.

Table IV. Adjusted analysis results for ELC, excluding patients with baseline evaluations done more than 3.5 months before HCT and those who underwent a second HCT

Covariate	Estimate (95% CI)	*P* value
Baseline ELC	0.82 (0.53 to 1.11)	<.001
Days in hospital	−0.32 (−0.60 to −0.05)	.020
No-ERT rate (per year)	−13.65 (−21.82 to −5.47)	.001
ERT rate (per year)	−3.63 (−7.59 to 0.33)	.072
Difference in rate, ERT versus no-ERT*	10.01 (0.94 to 19.09)	.031
Excluding deaths		
Baseline ELC	0.67 (0.48 to 0.85)	<.001
Days in hospital	−0.05 (−0.15 to 0.05)	.361
No-ERT rate (per year)	−9.18 (−12.74 to −5.63)	<.001
ERT rate (per year)	−3.51 (−7.28 to 0.27)	.068
Difference in rate, ERT versus no-ERT*	5.68 (0.59 to 10.76)	.029

*Difference calculated based on the estimated rate of each group.

Table II. Unadjusted ELC and domain T-scores across visit

Score	Baseline (before HCT)	One year post-HCT	Two years post-HCT
ELC*			
ERT	84.0 (15.0)	74.1 (11.3)	76.2 (14.2)
No-ERT	91.8 (18.5)	70.9 (12.5)	71.3 (12.8)
Visual Reception domain†			
ERT	40.6 (10.0)	38.0 (10.4)	46.0 (12.9)
No-ERT	48.4 (10.9)	35.2 (8.89)	33.5 (6.95)
Fine Motor domain†			
ERT	39.9 (9.75)	34.6 (7.63)	30.6 (9.44)
No-ERT	46.1 (11.6)	33.1 (7.03)	29.0 (11.6)
Receptive Language domain†			
ERT	39.7 (9.64)	39.7 (12.5)	38.9 (8.98)
No-ERT	39.0 (13.4)	36.1 (10.1)	35.3 (9.05)
Expressive Language domain†			
ERT	40.0 (8.66)	35.3 (10.1)	33.6 (9.19)
No-ERT	44.5 (10.9)	32.5 (10.4)	37.6 (8.85)

Values presented are mean (SD).
*Mean, 100 ± 15.
†Mean, 50 ± 10.

Table V. Adjustment for the reduced-intensity preparative regimen

Covariate	Estimate (95% CI)	*P* value
Baseline ELC	0.94 (0.55 to 1.32)	<.001
Days in hospital	−0.27 (−0.50 to −0.05)	.015
Special preparation	13.76 (−0.94 to 28.47)	.067
No-ERT rate (per year)	−12.94 (−20.38 to −5.50)	<.001
ERT rate (per year)	−3.56 (−7.62 to 0.49)	.085
Difference in rate, ERT versus no-ERT*	9.37 (0.92 to 17.83)	.030
Excluding deaths		
Baseline ELC	0.76 (0.51 to 1.01)	<.001
Days in hospital	−0.06 (−0.16 to 0.03)	.197
Special preparation	4.39 (−6.75 to 15.52)	.440
No-ERT rate (per year)	−8.97 (−12.15 to −5.80)	<.001
ERT rate (per year)	−3.49 (−7.35 to 0.36)	.076
Difference in rate, ERT versus no-ERT*	5.48 (0.61 to 10.35)	.027

*Difference calculated based on the estimated rate of each group.