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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Supported by University of Minnesota and Lysosomal Disease Network fellowship (NIH U54NS065768-01), and Children's Cancer Research Fund (CCRF), MN. J.E. has received travel support from Shire Pharmaceuticals. P.O. has received grants for unrelated MPS IH work from Genzyme and has served on the Genzyme speaker's bureau. CCRF provides financial support to the Blood and Marrow Transplant Service of the University of Minnesota, where P.O. and J.T. are faculty and T.K. is on the clinical service. E.S. has participated on the MPS Registry Board for Genzyme and has received grants from Genzyme, Shire, and Biomarin. C.W. has received grants from Actelion, Amicus, BioMarin, Fairview Hospitals, Genzyme, Pfizer, Protalix, and Shire; has served as a consultant for Actelion, BioMarin, Genzyme, Pfizer, Protalix, and Shire; has been a speaker for Actelion; and owns stock in Zebraic. K.R. and R.Z. declare no conflicts of interest.

Portions of this were presented as a poster session at the WORLD (We Organize Research on Lysosomal Diseases) Conference on lysosomal diseases, February 10-12, 2012, Miami, Florida.

0022-3476/$ - see front matter. Copyright © 2013 Mosby Inc. All rights reserved. http://dx.doi.org/10.1016/j.jpeds.2012.07.052

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).

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