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Reduced Intensity Conditioning and Hematopoietic Stem Cell Transplantation in Pediatric Nonmalignant Disease: A New Therapeutic Paradigm

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Hematopoietic stem cell transplantation (HSCT) has shown promising advances during the past 50 years and is presently a curative option for several pediatric diseases.[1] HSCT is often used as a treatment for recurrent or refractory malignancies,[2,3] but more frequently is seen as an early therapeutic option in many nonmalignant diseases (NMDs).[4] This is based on early successes such as severe combined immunodeficiency, where transplantation has an 80%-90% cure rate,[5,6] and severe aplastic anemia, where HSCT has supplanted immunosuppressive therapy for patients with a matched sibling donor.[7] Through direct replacement of cellular defects in the marrow or hematopoietic progenitor cells or the provision of circulating cells with normal enzymatic function to tissue where the enzyme is otherwise lacking, HSCT presents multiple attractive mechanisms to treat NMD.

Historically, HSCT is preceded by a myeloablative conditioning (MAC) regimen, which leaves the recipient susceptible to deleterious side effects.[8] Despite improvements in supportive care, there is a donor source–dependent, 10%-27% treatment-related mortality (TRM) secondary to pediatric HSCT.[9] Reported acute and chronic graft-versus-host disease (GVHD) rates are 56% and 33%, respectively.[9] Particularly distressing for pediatric HSCT recipients are the late effects of MAC, which can lead to decades of chronic health-related problems.[10-13] The National Cancer Institute summarized the late effects associated with pediatric HSCT recipients, including significantly greater rates of iron overload, chronic kidney disease, cardiac death, prolonged immunodeficiency, and endocrinopathies, including diabetes, growth impairment, osteopenia, and infertility.[10-13] The risk of such complications limited the use of HSCT as a cure for NMDs, especially when the natural history was not one of rapid fatality, but shortened lifespan and significant morbidity.[8] In diseases such as sickle cell disease (SCD) and thalassemia, where medical management can improve survival, the risk of toxicity associated with HSCT was seen by many as a contraindication to its use.[14]

The recognition that an immune response of the graft against the host's bone marrow played a significant role in the eradication of the underlying disease[15] lead the development of reduced-intensity conditioning (RIC) regimens.[16] Although RIC encompasses many chemotherapy and radiation regimens, it is generally characterized by reversible myelosuppression, reduced regimen-related toxicity, and greater incidence of mixed chimerism.[17] In multiple studies that compare MAC and RIC in different age groups and donor sources, investigators have shown decreased acute hematologic, gastrointestinal, renal, hepatic, and pulmonary toxicities, as much as a 2.6-fold decrease in GVHD, and stable-to-improved overall survival (OS) and TRM.[18,19] Our group also demonstrated unchanged engraftment and immune reconstitution rates in pediatric recipients of unrelated cord blood transplant (UCBT) preceded by RIC.[18]

Early concerns that RIC would necessitate intense immune suppression leading to increased rates of viral and invasive fungal infection have not come to fruition; infections with these organisms occur at equivalent rates to MAC.[20] The ability to achieve stable engraftment rates with decreased toxicity alleviates some of the earlier concerns regarding the use of HSCT in the nonmalignant patient population. The recent advances in RIC discussed herein lay the groundwork for a paradigm shift in the use of HSCT in pediatric NMDs (**Table**).

Rao et al[21] were able to show a significant survival advantage after the use of RIC and HSCT in children with primary immunodeficiencies. As these children often come to transplantation with significant comorbid infections, they may be the most vulnerable to the toxicity of MAC. Other measurable outcomes, including time to engraftment, chimerism, immune reconstitution, and GVHD were comparable, although RIC did have a greater rate of viral reactivation. The ability to decrease conditioning intensity in a risk-adapted manner was demonstrated by our group in children

GVHD	Graft-versus-host disease
HSCT	Hematopoietic stem cell transplantation
MAC	Myeloablative conditioning
NMD	Nonmalignant disease
OS	Overall survival
RIC	Reduced-intensity conditioning
SCD	Sickle cell disease
TRM	Treatment-related mortality
UCBT	Unrelated cord blood transplant

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Table. Summary of some of the most notable work to date highlighting the benefits of RIC HSCT in pediatric NMD

Author	No. patients	Diagnosis	Conditioning regimen (n)	Outcome
Satwani et al[4]	100	50 patients MD 50 patients NMD	Bu/Flu/alemtuzumab (35) Bu/Flu± r-ATG (45) Flu/Cy± r-ATG (20)	OS 72.9%, EFS 59.5%, GVHD 20%
Radhakrishnan et al[23]	8	High-risk SCD	Bu/Flu/alemtuzumab (8)	OS 62.5%, EFS 50% GVHD 50%
McGuinn et al[22]	18	Severe aplastic anemia	Flu/LDCy/r-ATG (8) Flu/HDCy/r-ATG (10)	OS 72%, EFS: not reported GVHD 34.4%
Rao et al[21]	52	Primary immunodeficiency syndromes	Flu/Mel/alemtuzumab (14) Flu/Mel/ATG (19) Bu/Cy + TCD (19)	OS 94% RIC vs 53% MAC EFS: not reported GVHD 9% RIC vs 10.5% MAC

Bu/Cy ± r-ATG, fludarabine150 mg/m^2, cyclophosphamide 60 mg/kg ± rabbit ATG 8 mg/kg; *Bu/Cy +TCD*, busulfan 16 mg/kg, cyclophosphamide 200 mg/kg, grafts were T-Cell depleted; *Bu/Flu/alemtuzumab*, busulfan 12.8-16 mg.kg, fludarabine 150-180 mg/m^2, alemtuzumab 54 mg/m^2; *Bu/Flu ± r-ATG*, busulfan 6.4-8 mg/kg, fludarabine 150 mg/m^2, ± rabbit ATG 8 mg/kg; *EFS*, event-free survival; *Flu/HDCy/r-ATG*, fludarabine 180 mg/m^2, cyclophosphamide 200 mg/kg and rabbit ATG 8 mg/kg; *Flu/Mel/ATG*, fludarabine 150 mg/m^2, melphalan 140 mg/m^2, ATG 12.5 mg/kg; *Flu/LDCy/r-ATG*, fludarabine 180 mg/m^2, cyclophosphamide 60 mg/kg and rabbit ATG 8 mg/kg; *Flu/Mel/alemtuzumab*, fludarabine 150 mg/m^2, melphalan 140 mg/m^2, alemtuzumab 1 mg/kg; *MD*, malignant disease.

and adolescents with severe aplastic anemia.[22] Patients were stratified into an intermediate- or high-risk group as determined by their previous transfusion history. Those patients with fewer than 10 transfusions were conditioned with a lower dose of cyclophosphamide without detriment to engraftment, donor chimerism, GVHD risk, or OS.

Satwani et al[4] evaluated 100 patients with both malignant and NMDs who received RIC HSCT. They were able to show that OS was unchanged from historical reports with MAC, but rates of acute GVHD and TRM were significantly decreased after RIC. One notable concern was the high rate of graft failure when UCBT was performed with RIC. They documented a 31.4% graft failure rate, which increased to 46.7% in patients who were chemotherapy-naïve and had a negative impact on OS in patients receiving UCBT. However, RIC before sibling bone marrow or cord blood transplantation in patients with high-risk SCD has resulted in 100% event-free survival and OS, low rates of acute GVHD, and complete engraftment.[23] The induction of donor chimerism after RIC HSCT in SCD is illustrated in the **Figure** (available at www.jpeds.com). The difference in outcome between UCBT and other stem cell sources may represent the most significant barrier to the use of RIC HSCT in pediatric NMD where limitations in donor options or the need to proceed to HSCT rapidly frequently preclude the use of a matched unrelated donor graft in this population. Even in metabolic diseases, where cord blood is the preferred stem cell source, RIC is still a risk factor for graft failure.[24]

At our institution, the use of human placental-derived stem cells to augment UCBT is being studied to try to improve engraftment and make unrelated cord blood a viable stem cell source for a patient population for whom alternative donor options are an absolute necessity (ClinicalTrials.gov: NCT01586455). Other alternative donor sources such as haploidentical or related nonsibling donors are currently in trials,[25] although their use with RIC is still limited. Finally, the advent of enzyme replacement and gene therapy in diseases such as adenosine deaminase–deficient severe combined immunodeficiency, Wiscott-Aldrich syndrome, and metachromatic leukodystrophy represents a promising future therapeutic option which may supplant transplantation in some disease.[26-28]

MAC HSCT has provided a lifesaving cure for children with a multitude of previously fatal or highly morbid conditions. However, this cure comes at the cost of lifelong morbidity associated with the use of highly toxic conditioning agents in a very young population.[10-13] The ability to minimize toxicity using RIC regimens provides a bright outlook for the future of HSCT in children with chronic NMDs. ■

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