

ADVANCES IN PEDIATRIC HEM/ONC

Current Developments in the Management of Childhood Malignancies

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Reduced-intensity Conditioning Allogeneic Stem Cell Transplantation in Pediatric Patients

Prakash Satwani, MD
Assistant Professor
Division of Pediatric Hematology
and Blood & Marrow Transplantation
Columbia University College of Physicians
and Surgeons
Morgan Stanley Children's Hospital
of New York-Presbyterian
New York, NY

H&O What is the concept behind reduced-intensity conditioning allogeneic stem cell transplantation?

PS The concept behind reduced-intensity conditioning (RIC) allogeneic stem cell transplantation (allo-SCT) is that instead of eradicating tumors through intensive/toxic chemoradiation, the stem cell donor's immune cells might be used for tumor eradication, relying on the allogeneic graft-versus-tumor and graft-versus-leukemia (GVL) effect.¹ However, in nonmalignant diseases, the aim of RIC allo-SCT is to create an immunologic platform of host and donor chimerism using pretransplantation and posttransplantation immunosuppression.

H&O When is RIC allo-SCT indicated in pediatric patients?

PS RIC allo-SCT has been performed in elderly adults for various malignant and nonmalignant diseases for over a decade. Elimination of high-dose cytotoxic conditioning therapy prior to transplantation can allow medically infirm patients to be treated with curative allo-SCT.¹ Children with malignant diseases who have significant

organ damage from previous chemotherapy, or who have a previous history of infections, are candidates for RIC allo-SCT. The goal in this group of children is to prevent not only early transplant-related mortality but also long-term morbidities. However, I believe the field must be advanced to include standard-risk patients as well, particularly those with immunodeficiencies or underlying genetic diseases. Once cured of underlying genetic defects, these children can have normal life expectancies. Without RIC allo-SCT, however, these children can sustain crippling, longstanding morbidities from myeloablative chemotherapy, which can affect quality of life (QOL).

H&O Is there any ongoing research into the use of this therapy in standard-risk patients?

PS We at Morgan Stanley Children's Hospital of New York-Presbyterian are conducting clinical trials of RIC enrolling standard-risk patients. We are trying to ascertain not only curative potentials of RIC allo-SCT but also short- and long-term toxicities in standard-risk patients. Studies of RIC allo-SCT are being conducted for children with sickle-cell disease, chronic myelogenous leukemia, standard-risk acute myeloid leukemia (AML), aplastic anemia, metabolic disorders, and autoimmune disorders.²

H&O What have been the findings regarding the treatment of pediatric acute lymphoblastic leukemia and AML with RIC allo-SCT?

PS RIC allo-SCT is intended to harness a GVL effect. There is substantial literature published providing evidence regarding the GVL effect in AML. However, the GVL effect is not well established in pediatric acute lymphoblastic leukemia (ALL). Our institution has not performed RIC allo-SCT in patients with ALL. At Children's Memorial Hospital in Chicago, 11 children with high risk ALL, who were ineligible for standard-intensity conditioning, received RIC allo-SCT. Of these, 36% of patients achieved remission. RIC transplant-related mortality, however, was high (50%).³ In another study

Table 1. Commonly Used Conditioning Regimens for Allogeneic Stem Cell Transplantation

Nonmyeloablative Regimens	Reduced-intensity Regimens	Myeloablative Regimens
2 Gy TBI 2 Gy TBI + FLU	CY (10–60 mg/kg) + FLU + ATG MEL (140 mg/kg) + FLU + ATG BU (≤8 mg/kg) + FLU + ATG BU (12.8–16 mg/kg) + FLU + ALEM	12–13.2 Gy TBI + CY (120 mg/kg) 12–13.2 Gy TBI + MEL (140–180 mg/kg) 12–13.2 Gy TBI + CY (120 mg/kg) + TT 12–13.2 Gy TBI + CY (120 mg/kg) + VP-16 BU (12.8–16 mg/kg) + CY (120 mg/kg) BU (12.8–16 mg/kg) + MEL (140–180 mg/kg)

ALEM = alemtuzumab; ATG = antithymocyte globulin; BU = busulfan; CY = cyclophosphamide; FLU = fludarabine; MEL = melphalan; TBI = total body irradiation; TT = thiotepa; VP-16 = etoposide.

at our institution, 8 pediatric patients with CD33-positive AML in first or second complete remission received targeted immunotherapy with gemtuzumab ozogamicin (Mylotarg, Wyeth-Ayerst) after allo-SCT during the time of potential minimal residual disease following RIC.⁴ RIC transplantation regimens were well tolerated without any significant morbidity or mortality and overall survival (63%) was comparable to that with the standard-intensity regimen

H&O How does the RIC regimen differ in various pediatric disease settings?

PS The incidence of primary graft failure following RIC allo-SCT can be as high as 20–25%.⁵ Children with malignant diseases who have received chemotherapy previously can achieve sustained donor chimerism with busulfan (6.4–8 mg/kg) and fludarabine (150–180 mg/m²) with or without antithymocyte globulin. However, heavily pretransfused pediatric patients or those receiving RIC allo-SCT for nonmalignant diseases using HLA-matched unrelated adult donors or unrelated cord blood transplantation are at a higher risk of graft rejection. It remains to be determined what degree of intensity is required for different pediatric subpopulations. Patients with primary refractory hematologic disease, including hemoglobinopathies, myelodysplastic syndromes (MDS), hemophagocytic lymphohistiocytosis, and/or severe aplastic anemia may require more intense conditioning and immunosuppression, particularly those patients who are heavily pretransfused.² Table 1 shows the commonly used reduced- and full-intensity conditioning regimens.

H&O What are the concerns regarding immune recovery with RIC allo-SCT?

PS The immune system of a patient who receives myeloablative allo-SCT is characterized by impaired immuno-

logic responses to recall antigens, as well as to mitogenic or allogeneic stimuli. This impairment predisposes them to various infections. Currently, there are no prospective data published in children that specifically document immune reconstitution following RIC allo-SCT. However, in adults, Bahceci and colleagues demonstrated that RIC allo-SCT may be associated with more rapid normalization of the T-cell repertoire and a significantly higher number of T cell receptor excision circle-bearing CD4- and CD8-positive cells.⁶ Immune reconstitution in children after RIC allo-SCT will vary depending upon pretransplantation and posttransplantation immune suppression, graft manipulation, and residual thymic activity. All of these factors should be considered regarding duration of antiviral and antifungal prophylaxis after RIC allo-SCT.

H&O Has there been research on QOL following RIC allo-SCT?

PS We compared QOL in 50 pediatric allo-SCT recipients and their parents following reduced-intensity versus ablative conditioning.⁷ In this study we demonstrated that children report different QOL than their parents do during the acute phase after transplantation (day 100–180), with children reporting higher levels of QOL. Children also report significantly improved QOL following RIC allo-SCT versus myeloablative SCT. Studies are ongoing to determine the trajectory of QOL over 2, 3, and 5 years, as well as whether QOL remains significantly improved following RIC.

H&O What data exist to support the use of allo-SCT over autologous transplantation in the pediatric setting?

PS Trials done in the past for patients with leukemia clearly demonstrated that allo-SCT is superior to autolo-

gous transplantation because the goal is to harness the GVL effect, which is not present with autologous transplantation. There are, though, certain pediatric conditions for which autologous transplantation is still the standard of care, such as high-risk or relapsed neuroblastoma. Despite double or triple tandem autologous transplant for high-risk neuroblastoma, the outcomes are still not optimal. We are conducting a study in high-risk neuroblastoma using autologous stem cell transplantation followed by RIC allo-SCT to assess whether there is any graft-versus-neuroblastoma effect.⁸ Similarly, for Hodgkin lymphoma in children, the standard of care remains autologous transplantation, but patients with this disease have a higher rate of relapse after the transplantation. Additionally, pediatric Hodgkin lymphoma patients are at risk of secondary malignancies and myelodysplastic syndromes due to heavy pretreatment before the procedure. We are also conducting a study in children with relapsed Hodgkin lymphoma; in this study autologous transplantation is followed by RIC allo-SCT.⁹ The aim of this sequence is to demonstrate not only GVL effect but also to reduce the risk of secondary leukemia and MDS.

H&O What are future directions for research of RIC allo-SCT in the pediatric setting?

PS Experience in children and adolescents with RIC allo-SCT is scant. Most of the studies are based on single-institution experience, with small heterogeneous groups of patients, variable conditioning regimens and immunosuppressive therapy, and short follow-up. The major impetus for performing RIC allo-SCT in children is to avoid the negative effects seen following myeloablative SCT: predisposition to growth failure, gonadal failure, secondary malignancies, and secondary MDS. However, to accurately determine the difference, if any, of late long-term effects in pediatric recipients following RIC allo-SCT, studies with a large cohort of patients with much longer follow-up are required. In the future, the role of consolidation after RIC allo-SCT with gemtuzumab ozogamicin for CD33-positive AML and imatinib mesylate (Gleevec, Novartis) for Philadelphia chromosome-positive leukemia to eradicate minimal residual disease should also be studied. Another question to answer is: is there any role for tailoring conditioning regimens (truly non-myeloablative versus reduced intensity versus myeloablative) according to cytogenetics, gene-expression profiling,

or the proteomics of malignant diseases? Furthermore, routine molecular monitoring of *BCR-ABL*, *PML-RAR α* , *WT1* gene transcripts might be helpful for the prediction and prompt management of relapse after RIC allo-SCT with donor lymphocyte infusion. There is a need for better therapy to prevent and treat graft-versus-host disease and for development of tools to monitor viral and fungal infection more efficiently.

Regardless of technical approaches to RIC allo-SCT, there is a fundamental requirement that controlled clinical trials be performed in children and adolescents with well-defined hematologic and nonhematologic malignancies in order to more fully evaluate the role of this procedure. The most appropriate candidates would be the patients with hematologic and nonhematologic malignancies who have failed initial therapies, who have a poor prognosis, and for whom salvage therapies exist that might be used for comparisons against RIC allo-SCT.

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