Rostrum

Radiation-sensitive severe combined immunodeficiency: The arguments for and against conditioning before hematopoietic cell transplantation—what to do?

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Defects in DNA cross-link repair 1C (*DCLRE1C*), protein kinase DNA activated catalytic polypeptide (*PRKDC*), ligase 4 (*LIG4*), *NHEJ1*, and *NBS1* involving the nonhomologous end-joining (NHEJ) DNA repair pathway result in radiation-sensitive severe combined immunodeficiency (SCID). Results of hematopoietic cell transplantation for radiation-sensitive SCID suggest that minimizing exposure to alkylating agents and ionizing radiation is important for optimizing survival and minimizing late effects. However, use of preconditioning with alkylating agents is associated with a greater likelihood of full T- and B-cell reconstitution compared with no conditioning or immunosuppression alone. A reduced-intensity regimen using fludarabine and low-dose cyclophosphamide might be effective for patients with *LIG4*, *NHEJ1*, and *NBS1* defects, although more data are needed to confirm these findings and characterize late effects. For patients with mutations in *DCLRE1C* (Artemis-deficient SCID), there is no optimal approach that uses standard dose-alkylating agents without significant late effects. Until nonchemotherapy agents, such as anti-CD45 or anti-CD117, become available, options include minimizing exposure to alkylators, such as single-agent low-dose targeted busulfan, or achieving T-cell reconstitution, followed several years later with a conditioning regimen to restore B-cell immunity. Gene therapy for these disorders will eventually remove the issues of rejection and graft-versus-host disease. Prospective multicenter studies are needed to evaluate these approaches in this rare but highly vulnerable patient population. (J Allergy Clin Immunol 2015;■■■:■■■-■■■.)

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Several DNA repair pathways have evolved to recognize and repair nonprogrammed DNA double-strand breaks (DSBs) resulting from ionizing radiation, alkylating agents, and/or replication errors.[1] DSBs activate ataxia-telangiectasia mutated and ataxia-telangiectasia and Rad3 kinases, which phosphorylate as many as 700 proteins that transduce the DNA damage signal, arrest the cell cycle, and start DNA repair or, if the damage cannot be repaired, activate apoptosis.[2,3] Unlike most other DNA damage, DNA DSBs directly threaten genomic integrity; thus these repair processes are essential for preserving genomic structure and reducing mutagenic risk and oncogenesis. Additionally, abnormal repair of DSBs can result in localized sequence abnormalities and loss of genomic information. More damaging is the joining of the wrong pair of DNA ends, resulting in deletions, translocations, or inversions.

Two pathways have evolved to repair DNA DSBs: homologous recombination (HR) and nonhomologous end joining (NHEJ).[1] HR functions primarily in dividing cells and the S phase and requires a homologous template to maintain replication accuracy. NHEJ can operate in dividing or nondividing cells, regardless of the cell-cycle phase, but is particularly used during phases of the cell cycle when a homologous template is not present. Unlike HR, NHEJ is an error-prone process with some loss of DNA information at the site of the DSB.

NHEJ also operates to repair damaged DNA after programmed DNA DSBs, which are critical for development of B- and T-lymphocyte receptor diversity associated with V(D)J recombination.[4] During T- and B-lymphocyte development, DSBs are introduced during lymphocyte antigen receptor development, immunoglobulin class-switch recombination, and somatic hypermutation. V(D)J recombination is initiated by enzymes coded by recombination-activating gene (RAG) 1 and RAG2, which form a complex that randomly introduces nicks in DNA by recognizing highly conserved sequences of DNA, recombination signal sequences, that flank all V, D, and J coding regions (Fig 1). Defects in RAG1 or RAG2 result in failure to initiate the V(D)J recombination process with subsequent failure to generate T and B lymphocytes and cause one variant of the most severe primary immunodeficiencies: T^-B^- natural killer (NK)–positive severe combined immunodeficiency ($T^-B^-NK^+$

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Abbreviations used
ART-SCID: Artemis-deficient severe combined immunodeficiency
ATG: Antithymocyte globulin
DNA-PKcs: DNA-dependent protein kinase catalytic subunit
DSB: Double-strand break
GvHD: Graft-versus-host disease
HCT: Hematopoietic cell transplantation
HR: Homologous recombination
HSC: Hematopoietic stem cell
MAC: Myeloablative conditioning
NHEJ: Nonhomologous end joining
NK: Natural killer
RAG: Recombination-activating gene
RIC: Reduced-intensity conditioning
SCID: Severe combined immunodeficiency
TBI: Total body irradiation

SCID). There are 5 other genes involved in V(D)J recombination that are in the NHEJ pathway and mutations of which cause $T^-B^-NK^+$ SCID: *DCLRE1C*, which codes for an endonuclease (Artemis); *PRKDC*, which codes for a phosphokinase (DNA-dependent protein kinase catalytic subunit [DNA-PKcs]); *LIG4*, which codes for DNA ligase 4; *NHEJ1*, which codes for Cernunnos; and *NBS1*, which codes for nibrin and is part of the MRE11 complex, which has a role in the end processing step in NHEJ along with Artemis and several other proteins.[4-8] The major distinction between RAG1/2-defective SCID and SCID associated with defects in the NHEJ pathway is that the NHEJ enzymes are ubiquitously found in all nucleated cells, such that fibroblasts and induced pluripotent stem cells from affected patients display general susceptibility to alkylating agents and ionizing radiation commonly used in conditioning regimens before allogeneic hematopoietic cell transplantation (HCT), whereas defects in RAG1/2 result in $T^-B^-NK^+$ SCID without increased susceptibility to alkylating agents and ionizing radiation.[9-11]

Patients with ataxia-telangiectasia have progressive neurodegeneration, combined T- and B-cell immunodeficiency, and an increased incidence of malignancy and increased sensitivity to ionizing radiation.[12] Although some improvement in the phenotype has been reported in *Atm*-deficient mice after HCT,[3] there is very limited experience with HCT in affected children, although there is at least one case report of a child with ataxia-telangiectasia and acute lymphoblastic leukemia surviving in remission for at least 3.5 years after matched sibling HCT.[13]

ARGUMENTS FOR AND AGAINST CONDITIONING

Controversy remains as to whether chemotherapy conditioning is required for normal immunoreconstitution after HCT for SCID.[14] When an HLA-matched sibling donor is used, the likelihood of T- and B-cell reconstitution, even without conditioning, is high regardless of the type of SCID,[15-17] although depending on the study and SCID genotype, this can vary from 47% to 81% of patients.[16,18] When an HLA-matched sibling is not available, alternative donors, such as haplocompatible relatives or unrelated volunteers or cord blood donors, are used. When closely matched unrelated donors are used without conditioning, depending on the SCID genotype/phenotype, T-cell rather than B-cell reconstitution is more likely, although graft-versus-host disease (GvHD) is a significant risk factor with unrelated donors, especially when serotherapy is not used.[18] T- and B-cell reconstitution can also vary with genotype. For example, patients with γc-SCID or JAK3-SCID easily engraft, with related haplocompatible T cell–depleted grafts fully reconstituting T-cell immunity but often without B-cell immunity,[17,19] whereas 60% to 70% of patients with RAG-deficient SCID or radiation-sensitive SCID reject these grafts when no conditioning is used and maternal chimerism is not present at the time of HCT.[19,20]

For the group of patients with maternal cells present at the time of HCT, it appears that use of the mother as the donor if an HLA-matched sibling or unrelated donor is not available can successfully reconstitute at least T-cell immunity without conditioning, although data are limited.[19] In one center's unpublished experience with $T^-B^-NK^+$ Artemis-deficient severe combined immunodeficiency (ART-SCID) or RAG-deficient SCID, 1 of 5 unconditioned recipients without maternal chimerism engrafted with a maternal donor and 8 of 8 patients with maternal cells engrafted with the mother as the donor, resulting in T-cell but not B-cell reconstitution, although the degree of T-cell reconstitution varied and often was incomplete (M. J. Cowan, personal communication). Interestingly, the patient with ART-SCID who engrafted without maternal chimerism present was treated with alemtuzumab as the only conditioning agent.[21] The mechanism for the engraftment of maternal cells in the presence of maternal chimerism before HCT has not been evaluated, although a possible explanation might be that the KIR receptor expression between the mother (donor) and child (recipient) favors engraftment.

When reduced-intensity conditioning (RIC) or myeloablative conditioning (MAC) is used, the likelihood of T- and B-cell reconstitution is increased significantly, regardless of the donor, as shown in a study of 240 patients with SCID undergoing transplantations in North America from 2000 through 2009.[16] In this study there were 136 infants surviving 2 to 5 years after HCT, of whom 54% had ceased gammaglobulin therapy. For those who were treated with RIC or MAC, there was an 84% (CI, 69% to 93%) chance of ceasing gammaglobulin supplementation versus a 41% (CI, 31% to 52%) chance for patients who received no conditioning or immunosuppression alone ($P < .001$). A similar observation was made regarding reconstitution of T-cell immunity as defined by a CD3 count of greater than 1000/mm^3 (ie, 89% [CI, 75% to 97%] for recipients of RIC or MAC vs 62% [CI, 51% to 73%] for recipients of none or immunosuppression alone; $P = .007$). However, it should be noted that even with conditioning, a not insignificant percentage of patients with SCID will still not fully reconstitute T-cell immunity, B-cell immunity, or both.

Exposure of infants to RIC or MAC is associated with some risk not only for potential late effects but also with respect to survival, particularly those patients with SCID who are infected at the time of HCT and those receiving a mismatched related donor with conditioning regardless of infection at the time of HCT. In the North American study age and infection at the time of transplantation were critical determinants of 5-year survival.[16] For those undergoing transplantation at less than 3.5 months of age, there was no significant difference in 5-year survival regardless of donor type, cell source, or conditioning versus no conditioning regimen. However, for patients who were infected at the time of HCT, the outcome was significantly better for