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Hematopoietic Stem Cell Transplantation for Severe Combined Immunodeficiency Diseases

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ABSTRACT

Hematopoietic stem cell transplantation (HSCT) is the only curative option for most children with severe combined immunodeficiency disease (SCID). Survival for SCID following HSCT has significantly improved over the past several decades, and ranges from 70% to 95% depending on the clinical condition of the child at the time of transplant, the availability of an HLA-matched sibling donor, and the SCID genotype/phenotype. In this article we will review the types of SCID and discuss the critical HSCT issues that confront us today, including the optimal source of donor cells when an HLA-matched sibling is not available, as well as the pros and cons of using conditioning therapy pretransplant. As SCID children have been followed for several decades, it is becoming apparent that long-term outcome and durable T and B cell immune reconstitution are quite variable depending on the initial treatment and source of donor cells. Finally, the development of methods to improve the early diagnosis of SCID along with designing prospective trials to evaluate the best approaches to curing these diseases with minimal toxicity are critical to improving outcomes for children with SCID.

KEY WORDS

Severe combined immunodeficiency (SCID) • Hematopoietic stem cell transplantation. Immune reconstitution • Newborn screening • Public health • Primary immunodeficiency • Genetic disease • Early diagnosis

INTRODUCTION

Although early results using gene therapy for some types of severe combined immunodeficiency diseases (SCID) are encouraging [1,2], hematopoietic stem cell transplantation (HSCT) remains the only curative option for most children with SCID. There has been a dramatic improvement in outcomes since the first transplants were done about 40 years ago, mostly as a result of significant advances in HLA typing, early recognition and diagnosis, genotyping, detection, and overall supportive care including detection and treatment of opportunistic infections. Today, children with SCID who are healthy at the time of transplant, who are recipients of HLA-matched donor transplants, and who do not require conditioning therapy can expect a better than 90% chance of long-term disease-free survival [2,3].

The major issues that confront us today involve (1) the durability of the stem cell graft and subsequent immune reconstitution, (2) donor selection when an HLA-matched sibling is not available and the type, and (3) intensity of conditioning regimens if one is necessary. With respect to the latter, an additional concern is potential long-term effects of conditioning therapy on these very young infants. As newborn screening for SCID becomes a reality, these issues become even more critical. Virtually all of the information that we have today regarding short- and long-term outcomes for children with SCID is the result of retrospective reports from either

single institutions or cooperative groups (EBMT or CIBMTR). The need for prospective randomized studies to evaluate some of these critical issues for children with SCID is obvious.

SCID GENOTYPES AND PHENOTYPES

Many genetic mutations involving critical proteins in DNA synthesis, T cell signaling, or V(D)J recombination have been identified as causing SCID [4]. These mutations result in several distinct phenotypes based upon the presence or absence of T, B, and NK cells. The most common cause of SCID results from mutations in the ILγc gene, and is seen in about 50% of all SCID cases. Generally, these children have the $T^-B^+NK^-$ phenotype, and presumably, because of the lack of NK cells, have durable T cell reconstitution without any conditioning therapy [5].

It is estimated that 20% of SCID is associated with the $T^-B^-NK^+$ phenotype, most commonly seen with a mutation in the RAG1 or RAG2 genes [6]. Another group of patients with $T^-B^-NK^+$ SCID is associated with mutations in genes coding for proteins involved in the nonhomologous DNA repair pathway, Artemis and Ligase IV [7-9]. Cells from these patients show increased sensitivity to ionizing radiation and alkylating agents. There is a high incidence of SCID secondary to a single point mutation in the gene that codes for Artemis among Athabascan speaking Native Americans in the Southwestern United States, in particular the Navajo and Apache Indians [8]. At least 1 study suggests that Navajo Indian children with SCID are particularly susceptible to treatment with alkylating agents, especially with respect to subsequent growth and development [10]. There is also at least 1 report of children with Artemis mutations who presented with EBV-related lymphomas, suggesting an increased susceptibility to cancer in this patient population [11]. Interestingly, these patients had incomplete Artemis mutations and a leaky SCID phenotype with some B cells present.

The other SCID phenotypes ($T^-B^+NK^+$ and $T^-B^-NK^-$) represent most of the remaining causes with a variety of defects that include ADA and PNP deficiency, IL7Rα defects, and defects in CD3δ, ϵ, and ζ, among others. There remains a less well-characterized group of SCID patients who present with T, B, and NK cells. Some of these patients have leaky mutations in genes such as RAG1/2 (Omenn's syndrome), Artemis, or ILγc; some are engrafted with maternal T cells, whereas the rest have no identified genotype to date.

ENGRAFTMENT AND IMMUNE RECONSTITUTION POST-HSCT

Because children with SCID have by definition absent to very low T cell immunity, it would be expected that they would be unlikely to reject a hematopoietic stem cell graft. There are 3 conditions in which engraftment and reconstitution of at least T cell immunity is likely to occur in this patient population even without immunosuppressive conditioning therapy: (1) when an HLA-matched related donor is available, (2) when maternal cells have engrafted in utero, or (3) when NK cells are absent. NK cells are thought to play a major role in graft resistance in children with SCID undergoing a haplocompatible transplant. However, regardless of the SCID phenotype, stem cells from HLA-matched sibling readily engraft without conditioning.

There are, however, reports of a gradual loss of T cell immunity based on thymic T cell receptor gene excision circle (TREC) output as well as T cell receptor diversity in patients with SCID who have not received conditioning [5,12]. This has led to some centers advocating the use of ablative therapy for all children with SCID undergoing a HSCT regardless of the phenotype or genotype. Of course, when unrelated donors are used, either adult volunteers or umbilical cord blood, ablative conditioning has generally been the rule [3,13]. The situation is further complicated by the fact that a subgroup of SCID patients have DNA repair defects that make them particularly susceptible to alkylating agents and ionizing radiation [10]. The paucity of data examining the late effects of conditioning on this particular patient population, most of whom are treated within the first year of life, further complicates the debate over the optimal approach for therapy.

ALTERNATIVE DONORS

When an HLA-matched related donor is not available there are 3 alternative sources that can be used: a haplocompatible relative, HLA-matched unrelated adult volunteer, or an unrelated banked UCB unit. Although most of the experience with alternative donors has been with haplocompatible relatives, there is a growing use of unrelated donors, either adult volunteers or cord blood [3,13,14]. There are advantages and disadvantages to each alternative donor source and unfortunately, because all of the reports to date have been historic retrospective comparisons it is virtually impossible to determine which approach might be optimal. Almost all of the transplants using unrelated donors have employed either full myeloablative or reduced intensity RIC regimens, whereas many of the haplocompatible donor studies have not used conditioning, at least as the initial transplant approach. This could certainly affect results of engraftment efficiency, T and B cell reconstitution, and late effects. The major concerns regarding the use of haplocompatible donors are the rejection rate, the relative delay in T cell recovery, and the loss of naïve