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Survey on Re-transplantation Criteria for Severe Combined Immunodeficiency Patients

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To the Editor

Although hematopoietic stem cell transplantation (HCT) has been an accepted life-saving therapy for severe combined immunodeficiency (SCID) for over 40 years, with progressive improvement in 10-year survival rates,^{1, 2} there is a lack of consensus as to best approaches. In particular, in these young and vulnerable patients, there is a well-founded desire to use no or minimal conditioning prior to transplantation. In spite of their immunodeficiency, however, SCID patients may manifest graft rejection or loss. The definition(s) of graft failure, and the indication(s) for delivery of a “boost” (defined as additional graft from the same donor without conditioning)² or re-transplantation (defined as additional graft from either the same or a different donor with conditioning) have been the subject of keen debate among transplant physicians caring for these patients.

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At workshops of the Primary Immune Deficiency Treatment Consortium (PIDTC), which represents 33 centers in North America,³ it became evident that different centers have individual approaches to re-transplantation for SCID patients, particularly with respect to indication, and when and how to re-transplant. With the aim of better defining these criteria, we conducted a survey among 20 North American and 5 European transplant centers to elicit feedback about their policy and experience on these issues. In this survey we considered two clinical situations in which re-transplantation may be considered: 1) graft failure; and 2) persistent immune dysfunction despite stable engraftment. Since the approach to HCT differs from center to center, we sought to determine the criteria used to define graft failure based on six proposed situations: no conditioning regimen (CR), reduced-intensity conditioning (RIC), and full myeloablative conditioning (MAC), for each of which transplantation with or without T-cell depletion (TCD) was considered. The survey was meant to capture policy at each center for patients with typical SCID.⁴

The survey

The questionnaire (designed by EH, MC and LN and sent to each center) was completed by the Principal Investigator (PI) of each center. To define graft failure, each PI was asked to respond to closed-ended questions based on the conditioning regimen in use at that center. Center PIs were given the choice of various criteria for defining the absence of T cell engraftment and the absence of myeloid engraftment. For persistent immune dysfunction despite stable engraftment, the survey included both open- and closed-ended questions and did not take into consideration the CR/TCD regimen used (see Online Repository E1). The center PIs who reported that SCID patients with persistent immune dysfunction despite T cell engraftment were not considered for re-transplantation at their center were asked to not respond to further questions.

Graft failure

Most centers selected “undetectable CD3⁺ T cells” or “absence of donor T-cell chimerism” to define the absence of donor T-cell engraftment, and “ANC < 500/ul” or “ANC > 500 but no donor myeloid cells detected” to define the absence of myeloid engraftment. As expected, in the absence of a CR, most centers considered lack of T cell engraftment as the only criterion needed to define graft failure post-HSCT (Table 1). Surprisingly, approximately 1/3 of the center PIs included the absence of myeloid engraftment as an additional criterion for graft failure even though without myeloablation, myeloid engraftment is unlikely. After a full MAC or RIC regimen, most centers (around 60%) required lack of both T-cell and myeloid engraftment as criteria for defining graft failure. In contrast, depending on the CR (MAC or RIC) and the presence or absence of TCD, 10 to 20% and 21 to 40% of the centers considered that lack of T-cell engraftment alone or myeloid engraftment alone, respectively, were sufficient to define graft failure (Table 1).

The interval needed to define lack of T-cell engraftment post-transplant was 2.00–2.36 months (median = 2 months) for HCT without TCD, and 3.00–3.63 months (median = 3 months) for HCT with TCD, independent of the regimen. In contrast, absence of myeloid engraftment post-HSCT was defined between 1–2 months (median) for MAC or RIC, independent of using TCD in either regimen. Importantly, despite the general trends illustrated (Table 1), the exact criteria used to define graft failure varied widely among the individual centers. For instance, some centers defined graft failure at 1 month as the absence of myeloid engraftment, whereas other centers defined it as the absence of T-cell engraftment at 6 months after HCT.

Persistent immune dysfunction despite stable engraftment

Since some patients may have persistent immune dysfunction despite stable engraftment,^{5–7} we evaluated the criteria used at each center to define poor immune reconstitution; and if, when and how SCID patients with persistent immune dysfunction should be re-transplanted. Overall, 23/25 centers confirmed that SCID patients with donor T-cell chimerism but persistent immune dysfunction would be considered for re-transplantation. Center PIs identified biological evidence of T cell dysfunction (21/23), recurrent/severe infections (16/23), and autoimmunity (10/23) as the main criteria for considering re-transplantation (Table 2). There was a reasonable agreement among centers on the definition of T cell dysfunction (Table 2).

Interestingly, even though 21/23 center PIs selected T-cell dysfunction as the main criterion for re-transplantation, only 12/23 responded that isolated T-cell dysfunction without clinical signs would be sufficient to consider re-transplantation, and 11/23 PIs reported that second transplants would require that T-cell dysfunction be associated with clinical signs of recurrent infections and/or autoimmunity. Twenty-one centers out of 23 responded that they would use the same donor (if available) for re-transplantation, and in such case, 12/21 would consider using a CR. By contrast, 5 center PIs reported they would not use a CR, and 4 responded the decision to use a CR would depend on additional criteria, such as chimerism, presence of infection, and/or type of donor. Almost all center PIs (20/23) considered that re-transplantation with a different second donor should be performed with a CR. There was lack of consensus regarding the timeframe for performing re-transplantation, since 9/23 centers reported that it was not a question of time, while among the other 14 centers, the majority answered within 1 year (n=8), and fewer centers (n=3) indicated within a time frame of 2 years post-HCT. Finally, in response to an open-ended question, most centers indicated that decisions regarding re-transplantation in this context are very difficult, and that it is hard to define criteria.

Conclusions

This survey shows that despite some trends, there is lack of consensus on criteria to define graft failure or indications for re-transplantation of patients with typical SCID who attain poor immune reconstitution. To-date, few studies^{1,5,7} have investigated the details of long-term clinical and immunologic function for SCID patients post-HCT. The quality of the immune reconstitution may vary depending on the molecular defect of the patient, for instance T-cell reconstitution is better in B⁺SCID than in B⁻SCID⁵ and functional B cell reconstitution is better if there is donor B cell engraftment in case of X-linked and JAK-3 SCID.^{8,9} However, only formal prospective and retrospective studies, such as those ongoing from the PIDTC,^{3,4,10} will be able to demonstrate the impact of specific molecular defects on immune reconstitution, better delineate the clinical and laboratory markers of poor immune reconstitution, and compare the impact of re-transplantation or not on overall survival of patients with poor immune reconstitution.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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The following centers contributed to the survey:

North American Centers: CHU Sainte-Justine, Montreal, Quebec, Canada; Children's Hospital Boston, MA; UCSF Benioff Children's Hospital, University of California, San Francisco, CA; Baylor College of Medicine, Houston, TX; Children's Hospital Los Angeles, Los Angeles, CA; The Children's Hospital of Philadelphia, Philadelphia, PA; Children's Memorial Hospital, Chicago, IL; Cincinnati Children's Hospital Medical Center, Cincinnati, OH; Duke University, Durham, NC; Memorial Sloan-Kettering Cancer Center, New York, NY; Cardinal Glennon Children's Medical Center, St Louis, MO; University of Utah, Salt Lake City, Utah; University of Michigan, Ann Arbor, MI; University of Alabama at Birmingham, Birmingham, AL; University of Texas Southwestern Medical Center, Dallas, TX; Children's National Medical Center, Washington, DC; Doernbecher Children's Hospital, Portland, OR; Methodist Children's Hospital of South Texas, San Antonio, TX; Stanford University, Stanford, CA; Children's Healthcare of Atlanta, Atlanta, GA.

European Centers: Hopital Necker-Enfants Malades, Paris, France; Universitäts-Kinderklinik, Ulm, Germany; The Queen Silvia Children's Hospital, Gothenburg, Sweden; Great Ormond Street Hospital, London, UK; Newcastle General Hospital, Newcastle, UK.

Abbreviations

SCID	severe combined immunodeficiency disease
CR	conditioning regimen
RIC	reduced-intensity conditioning regimen
MAC	myeloablative conditioning regimen
TREC	T cell receptor excision circle

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Table 1

Definition of Graft Failure after HSCT for SCID Patients

HSCT regimen	T cell criteria only	Myeloid criteria only	Myeloid and T cell criteria			T cell criteria timeframe post-HSCT	Myeloid criteria timeframe post-HSCT
			T cell and myeloid criteria at the same time	Myeloid criteria followed by T cell criteria	T cell criteria followed by myeloid criteria		
Centers performing transplantation without conditioning (No CR):							
No CR (N=24) *	16 (66%)	-	8 (33%)	-	-	2 months (median 2 months)	-
No CR + TCD (N=15) *	11 (73%)	-	4 (27%)	-	-	3.63 months (median 3 months)	-
Centers performing transplantation with reduced-intensity conditioning (RIC):							
RIC (N=21) *	6 (29%)	2 (9.5%)	2 (9.5%)	9 (43%)	2 (9%)	2.36 months (median 2 months)	1.93 months (median 2 months)
RIC + TCD (N=10) *	4 (40%)	-	2 (20%)	4 (40%)	-	3.4 months (median 3 months)	1.83 months (median 2 months)
Centers performing transplantation with full myeloablative conditioning (MAC):							
MAC (N=19) *	4 (21%)	3 (16%)	5 (26%)	7 (37%)	-	2.25 months (median 2 months)	1.6 months (median 2 months)
MAC + TCD (N=14) *	4 (29%)	2 (14%)	1 (7%)	7 (50%)	-	3.25 months (median 3 months)	1.4 months (median 1 months)

* N: number of centers performing the regimen and responding to the question. This explains that while a total of 25 centers participated in the survey, the denominator for total N in many categories is less than 25.

Abbreviations: HSCT, hematopoietic stem cell transplantation; CR, conditioning regimen; RIC, reduced-intensity conditioning; MAC, myeloablative conditioning; TCD, T cell depletion

Table 2

Criteria for Re-transplantation after Stable Engraftment but Persistent Immune Dysfunction

Criteria	No of Centers selecting the response (N=23 total)*
Laboratory evidence of T-cell dysfunction Defined as:	21
• CD3 ⁺ T-cell count < 500/mm ³	15
• T-cell proliferation to mitogen < 20% of lower limit of controls	12
• T-cell proliferation to antigens < 10% of lower limit of controls	10
• Oligoclonal T-cell repertoire	9
Other:	7
• CD3 ⁺ T-cell count < 200/mm ³	1
• Poor TREC equivalent or absence of naïve T-cell count	2
• CD4 ⁺ T-cell count < 100/mm ³	1
• Low T cells with infections	1
• Infections in general	1
• “Whole clinical picture”	1
B-cell dysfunction (absent antibody production)	2
Autoimmunity	10
GvHD	3
Infections (new or failure to clear infection)	16
Absence of myeloid engraftment	4
Other clinical or laboratory criteria:	
• Chronic pulmonary disease	1
• CD45RA ⁺ T cell, TRECs	1
• Growth failure	1

* N=23: Only 23 centers (among 25 participating) confirmed that SCID patients with T cell chimerism but persistent immune dysfunction could be considered for re-transplantation and only these centers continued the survey