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Reviews

Will Post-Transplantation Cell Therapies for Pediatric Patients Become Standard of Care?

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A B S T R A C T

Although allogeneic hematopoietic stem cell transplantation (HSCT) is a curative approach for many pediatric patients with hematologic malignancies and some nonmalignant disorders, some critical obstacles remain to be overcome, including relapse, engraftment failure, graft-versus-host disease (GVHD), and infection. Harnessing the immune system to induce a graft-versus-tumor effect or rapidly restore antiviral immunity through the use of donor lymphocyte infusion (DLI) has been remarkably successful in some settings. Unfortunately, however, the responses to DLI can be variable, and GVHD is common. Thus, manipulations to minimize GVHD while restoring antiviral immunity and enhancing the graft-versus-tumor effect are needed to improve outcomes after allogeneic HSCT. Cellular therapies, defined as treatment modalities in which hematopoietic or nonhematopoietic cells are used as therapeutic agents, offer this promise for improving outcomes post-HSCT. This review presents an overview of the field for pediatric cell therapies in the transplant setting and discusses how we can broaden applicability beyond phase I.

INTRODUCTION

Cellular therapies have been developed primarily as therapeutic agents to treat malignancies, infections in immunocompromised hosts, and inflammatory disorders. Minimally manipulated products, such as donor lymphocyte infusion (DLI), involve a manufacturing process that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement. In contrast, if the biological characteristics of the cells change during the processing, then the cells are more than minimally manipulated. In this review, we focus on complex cellular therapies that require more than minimal manipulation. To date, the clinical experience with novel cell therapeutics to treat pediatric patients after allogeneic hematopoietic stem cell transplantation (HSCT) generally has been restricted to phase I/II pediatric or combined studies (Table 1). This review presents an overview of the field in pediatric cell therapies after HSCT and then discusses how we can move these therapies from investigational status to the standard of care by moving beyond phase I to more definitive clinical trials.

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Table 1
Adoptive Cellular Therapy Studies after HSCT in Pediatric Patients

Cellular Therapy	References	Pediatric or Combined Study	Key Findings
Virus-specific CTLs			
EBV	Doubrinova et al. [8]	Combined	Efficacy of donor EBV CTLs in EBV-LPD
	Comoli et al. [10]	Pediatric	Efficacy of donor EBV CTLs in $CD19^+/CD20^-$ EBV-LPD after rituximab
	Icheva et al. [11]	Combined	Efficacy of EBNA1-specific donor CTLs in EBV-LPD
CMV	Feuchtinger et al. [18]	Pediatric	Safety and efficacy of donor CMV CTLs using pp65 protein stimulation/IFN-γ selection
	Meij et al. [20]	Combined	Safety and efficacy of donor CMV CTLs using pp65 peptide stimulation/IFN-γ selection
AdV	Feuchtinger et al. [26]	Pediatric	Safety and efficacy of AdV-specific CD4/CD8 donor T cells using protein stimulation/IFN-γ selection
Multivirus	Leen et al. [28]	Pediatric	Safety and in vivo persistence of EBV- and AdV-bispecific donor CTLs after HLA-mismatched HSCT
	Gerdemann et al. [19]	Combined	Safety and efficacy of trivirus-specific CTLs generated using DC nucleofection technology
	Papadopoulou et al. [29]	Combined	Safety and efficacy of single-culture virus-specific T cells recognizing 12 immunogenic antigens from AdV, CMV, AdV, BK and HHV6
Third-party	Leen et al. [33]	Combined	Multicenter study demonstrating the feasibility and efficacy of banked third-party virus-specific CTLs
NK cells	Stern et al. [55]	Combined	Feasibility and safety of purified ($CD3^-/CD56^+$) donor NK cell infusions after haploidentical HSCT
	Rubnitz et al. [58]	Pediatric	Safety and engraftment of KIR ligand-mismatched haploidentical purified ($CD3^-/CD56^+$) NK cells in AML
	Brehm et al. [59]	Pediatric	Difference in efficacy of nonstimulated versus IL-2–stimulated purified ($CD3^-/CD56^+$) NK cells after haploidentical HSCT
	Kloess et al. [56]	Pediatric	Efficacy of IL-2–stimulated NK cells after haploidentical HSCT in neuroblastoma and role of soluble MICA
CIK cells	Rettinger et al. [68]	Pediatric	Safety and feasibility of IL-15–stimulated donor CIK cells after haploidentical HSCT
CAR T cells	Grupp et al. [91]	Pediatric	First report on safety and remission induction of autologous CD19.CAR T cells in ALL
	Cruz et al. [93]	Combined	Safety and efficacy of allogeneic virus-specific CD19.CAR T cells
	Grupp et al. [98]	Pediatric	Efficacy and management of CRS after treatment with autologous and allogeneic CD19.CAR T cells
MSCs (acute GVHD)	LeBlanc et al. [124]	Pediatric	First report of successful remission induction by MSC treatment in a child with refractory GVHD
	LeBlanc et al. [125]	Combined	Multicenter study showing feasibility, safety and efficacy of fetal bovine serum expanded MSCs in GVHD
	Lucchini et al. [126]	Pediatric	Safety and efficacy using platelet-lysate expanded MSCs in steroid-refractory GVHD
	Ball et al. [127]	Pediatric	Multicenter study showing feasibility and efficacy of MSCs in steroid-refractory GVHD grade III-IV
	Introna et al. [128]	Combined	Multicenter study reporting feasibility and efficacy in of MSCs in steroid-refractory GVHD grade II-IV
	Prasad et al. [129]	Pediatric	Report on clinical outcome using the Prochymal MSC product in steroid-refractory GVHD grade II-IV

OVERVIEW OF CURRENT CELLULAR THERAPIES

Virus-Specific T Cells

Viral infections are a major cause of morbidity and mortality after HSCT. Given that the recovery of virus-specific T cells is clearly associated with protection from viral infection, adoptive immunotherapy to decrease the time to immune reconstitution or to treat viral reactivations and infections is an attractive approach. The majority of T cell studies in pediatrics have focused on cytomegalovirus (CMV), Epstin-Barr virus (EBV), and adenovirus (AdV) and trials of donor-derived cytotoxic T lymphocytes (CTLs) specific for single viruses [1]. Although methodologies have been developed and clinical trials evaluating T cells specific for other viral pathogens, such as BK virus, human herpesvirus 6, and varicella zoster, have shown promising results, the patient numbers are still relatively small. In contrast, T cell therapies aimed at reconstituting EBV-specific T cell immunity have been used for almost 20 years [2-5], In the first reported studies, unmanipulated DLIs were administered to pediatric HSCT recipients with established disease or falling donor chimerism [6,7]. Although effective in some patients, this approach has limited efficacy, however, and is further limited by the presence of alloreactive T cells in the DLI product and the resultant potential for graft-versus-host disease (GVHD), which led to the development of donor-derived EBV-specific T cells for clinical use [7-9]. Although many of the studies using EBV-specific T cells were conducted during the pre-rituximab era, there are still an appreciable number of pediatric patients with rituximab-resistant disease that is responsive to EBV-specific T cells [10]. The results of these studies confirm that donor-derived EBV-specific CTL therapy is safe and effective when used either as prophylaxis or as treatment for EBV-mediated post-transplantation lymphoproliferative disease after HSCT, and this approach is now focused on rapid manufacturing using sorting strategies with HLA-peptide multimers or IFN-γ capture [11-13].

The administration of CMV-specific T cells after HSCT was first explored by Walter et al. [14] and Riddell et al. [15], who infused donor-derived CMV-specific $CD8^+$ clones to recipients of matched sibling donor grafts. Numerous groups have built on these initial studies of CMV-specific T cell