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Educational Reviews

Reprint of: Virus-Specific T Cells: Broadening Applicability ☆

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Virus infection remains an appreciable cause of morbidity and mortality after hematopoietic stem cell transplantation (HSCT). Although pharmacotherapy and/or antibody therapy may help prevent or treat viral disease, these drugs are expensive, toxic, and often ineffective due to primary or secondary resistance. Further, effective treatments are limited for many infections (eg, adenovirus, BK virus), which are increasingly detected after alternative donor transplants. These deficiencies in conventional therapeutics have increased interest in an immunotherapeutic approach to viral disorders, leading to adoptive transfer of virus-specific cytotoxic T lymphocytes (VSTs), which can rapidly reconstitute antiviral immunity post-transplantation without causing graft-versus-host disease. This review will explore how the VST field has improved outcomes for many patients with life-threatening viral infections after HSCT, and how to broaden applicability beyond the "patient-specific" products, as well as extending to other viral diseases even outside the context of HSCT.

INTRODUCTION

It is more than 26 years since the first proof-of-principle studies conducted by Riddell et al. demonstrated that virus-specific T cell clones from a healthy donor could be generated ex vivo from autologous cytomegalovirus (CMV)-infected fibroblasts. When adoptively transferred into an allogeneic hematopoietic stem cell transplantation (HSCT) recipient, these virus-specific T cells (VSTs) could prevent CMV infection without causing graft-versus-host disease (GVHD) [1]. Since then, numerous trials of adoptive immunotherapy with VSTs derived from transplant donors have established their safety and potency for both the prevention and treatment of CMV disease. Application of VST has subsequently expanded, first to the generation of Epstein-Barr virus (EBV)-specific T cells [2-4] and then to the generation of multivirus-specific T cells targeting common post-transplantation viral pathogens, including adenovirus, BK virus, and human herpesvirus type 6 [2,5]. These studies indicated that the techniques used to elicit VSTs could successfully be applied to numerous viruses.

Central to the development and application of VSTs has been technology-based progress in the generation of VSTs. Historically, the process required a lengthy, 8- to 10-week culture period. In the process of optimization, which notably includes the use of gas-permeable culture flasks for rapid T cell expansion, the technique has become simpler and cheaper. Today, it is possible to generate VSTs from autologous antigen-presenting cells pulsed with viral peptide libraries in less than 14 days. More recently, groups have used T cells isolated directly from donor leukocytes on the basis of their binding viral peptide/HLA tetramers or dissociable streptamers, or on expression of activation markers or cytokines after short-term in vitro sensitization [2]. Despite these efforts to speed VST production, the acute nature of viral illness in immunosuppressed individuals often demands immediate availability of the T cell product. Furthermore, viruses complicating organ transplantation, such as EBV, present a particular problem for adoptive T cell transfer therapies. Although immunosuppressed, organ transplant recipients, in contrast to HSCT recipients, are not tolerant of adoptively transferred T cells, even if the cell donor is HLA-matched. These contingencies have spurred the development of banked off-the- shelf VST products. Select closely HLA-matched cell products can be shipped for same-day use. Despite the challenges, however, such third-party donor VST banks are being developed, as we discuss in this review.

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Finally, successful management of post-HSCT viral complications has stimulated research into the treatment of viral diseases outside the context of HSCT. VSTs are now being explored in a broad range of inherited and acquired immunodeficient states. Here we review the latest approaches for generating VSTs for these new indications and the results of clinical trials in transplantation- and non-transplantation-related polyomavirus and human immunodeficiency virus (HIV) infections.

THIRD-PARTY VSTS

The principal constraints to the broader application of adoptive therapy with transplant donor-derived T cells are logistic in nature. The relatively low incidence of refractory infectious complications in the post-transplantation period makes it impractical to generate viral-specific populations for all HSCT recipients at risk. At the same time, the aggressive nature of these infections requires rapid treatment of patients who do not respond to first line antiviral therapy. Thus, an 8- to 10-week wait is too long once a patient has been identified as needing treatment. Therefore, the use of longer manufacturing approaches means that T cells need to be generated before the patient develops an infection. Although recent approaches bypass this constraint, rapid selection of low-frequency populations of T cells might not be possible. Some of the limitations in the generation and application of donor-derived viral-specific adoptive cell therapy can be overcome by using banked, off-the shelf, or so-called third-party T cells.

Limitations of Viral Capture Strategies

Rapid selection by tetramer or streptamer depends on identifying an HLA allele and the viral epitope presented by that HLA allele. Variants of prevalent HLA alleles differ in the capacity to present specific viral epitopes, making it challenging to use this capture method of selection for patients not bearing common HLA alleles. Other logistic constraints include the fact that some donors may be unwilling or unable to provide the secondary donations needed to generate VSTs. In addition, although possible, it is difficult to generate viral-specific populations from donors who have not been previously sensitized to the virus in question.

HLA Restriction

More critical to the efficacy of VSTs generated from the HCT donor is the issue of HLA restriction. In the HLA-nonidentical transplant setting, viral-specific cytotoxic T lymphocytes (CTLs) may be restricted in cytotoxicity through an HLA allele not shared by the HCT recipient and thus ineffective in treating host infected targets. This issue is especially problematic if the VST line is not assessed for HLA restriction before infusion. With the increased use of haploidentical HCT donors, the issue of ensuring appropriate HLA restriction of VSTs will become paramount. These limitations, and an attempt to provide access to VSTs for a growing number of centers, have led groups at Baylor College of Medicine, Children's National Medical Center, University of Edinburgh, Memorial Sloan Kettering Cancer Center (MSKCC), and University of Tubingen to explore the use of banked partially HLA-matched viral-specific CTLs derived from third-party donors (eg, healthy individuals other than the HCT donor or the patient). This approach has now gained traction and is being attempted by a growing number of centers [2].

Treatment of Post-Transplantation Lymphoproliferative Disease

As pioneered by Dorothy Crawford and reported by Haque et al. [3], the group at the University of Edinburgh used partially HLA-matched EBV-specific T cells derived from a bank of 70 lines generated from healthy EBV-seropositive volunteer blood donors to treat 33 solid organ transplant patients with EBV post-transplantation lymphoproliferative disease. In this study, 52% of patients achieved a complete response or partial response that was sustained for ≥6 months. Since that time, other groups have expanded this experience to treat an expanding number of viral infections primarily in HCT recipients. These centers include, but are not limited to, Children's National Medical Center, the University of Aberdeen, Baylor College of Medicine, The Karolinska Institute, The University of Tubingen and MSKCC. Reports on fewer than 200 HSCT recipients treated with third-party VSTs confirm the potential efficacy and limited risk of toxicities, including GVHD [4].

Clinical Experience with VST Cell Banks

Banks of appropriate diversity have been generated and in addition to their immediate accessibility, these banks of third-party donor-derived VSTs provide unique advantages for recipients of HLA nonidentical HSCT. Because banked T cells are characterized by their HLA restriction, T cells restricted by an HLA allele expressed by the virus-infected cells in the patient can be selected. Indeed, in a survey of consecutive transplant recipients at MSKCC, from a bank of 132 GMP grade CMVpp65-specific T cell lines, we could identify appropriately restricted lines for 93% of HLA-nonidentical HSCT recipients and 98% of cord blood transplant recipients. In contrast, examination of the HLA restrictions of CMVpp65-specific T cells generated from the donors of HLA-nonidentical HSCT grafts showed that they were restricted by an HLA shared by the transplant recipient in only 60% to 70% of cases [4]. Working with a more limited bank, the group at Baylor demonstrated that a bank of just 32 tri-VST lines was sufficient to provide suitable HLA-restricted T cells for 90% of the patients referred for treatment in their multicenter trial [2]. More recently, they treated 38 patients with multiple viral infections from a bank of 59 lines generated with specificity for adenovirus, BK virus, CMV, EBV, and human herpesvirus 6 [5]. A third advantage is that certain patients may fail to respond to VSTs specific for epitopes presented by one HLA allele and may respond to treatment with T cells from a different third-party donor specific for a different epitope presented by a different shared HLA allele.

Adoptively transferred third-party T cells have a demonstrated role in the initial responses observed. However, the durability of responses is both surprising and unexplained. Transplant donor-derived VSTs persist long-term. Indeed, as reported by Heslop et al. [6], the group at Baylor detected genetically marked donor-derived EBV-specific T cells as long as 10 years after adoptive transfer. In contrast, third-party T cells, although detected for as long as 90 days after infusion into immunodeficient HSCT recipients, do not achieve durable engraftment [4]. Nevertheless, the responses induced are usually sustained even in patients who are still markedly lymphopenic.

The mechanisms contributing to the sustained responses observed are unknown. It is possible that the initial transient expansion of VSTs is sufficient to control asymptomatic latent infections. Small numbers of the third-party T cells may persist long enough at sites of infection to sustain control until