

POINTS TO CONSIDER

TECHNICAL ABSTRACT

Closely HLA-Matched Allogeneic Virus Specific Cytotoxic T-Lymphocytes (CTL) to Treat Persistent Reactivation or Infection with Adenovirus, CMV and EBV after Hemopoietic Stem Cell Transplantation (HSCT)

Study Design: The primary purpose of the study is to evaluate whether closely HLA-matched multivirus specific CTL lines obtained from a bank of allogeneic viral specific cell lines have antiviral activity against three viruses: EBV, CMV and adenovirus. Reconstitution of anti-viral immunity by donor-derived CTLs has shown promise in preventing and treating infections with CMV, EBV and adenovirus post-hemopoietic stem cell transplant (HSCT). However, the time taken to prepare patient-specific products and lack of virus-specific memory T cells in cord blood and seronegative donors, limits their value. An alternative approach that bypasses the need to grow CTLs for individual patients is to bank closely HLA-matched allogeneic cytotoxic T lymphocyte lines (CHM-CTLs) that could be available as an "off the shelf" product. A concern with this approach is that the in vivo persistence of a mismatched product may be suboptimal after administration, as the recipient may generate an immune response to the non-shared HLA antigens. However, a number of small studies showed the feasibility of this approach and reported clinical responses in the patients with EBV lymphoma arising after HSCT or solid organ transplant which was confirmed in a recently reported Phase II study from Haque and colleagues. This approach, therefore, warrants further evaluation. In this protocol we propose to evaluate if using closely matched allogeneic CTLs is a safe and feasible strategy for treating patients post-HSCT with CMV, adenovirus or EBV infection persistent despite standard therapy. We will manufacture CTLs specific for CMV, adenovirus and EBV from normal eligible donors by stimulating peripheral blood mononuclear cells with monocytes and EBV-transformed LCLs transduced with an Ad5/35 vector encoding the CMV-derived pp65 antigen. After passing QC testing the allogeneic cytotoxic T lymphocyte lines (CHM-CTLs) will be available for administration to subjects who have persistent viral infection and match at least one HLA antigen. The study agent will be assessed for safety (stopping rules defined) and antiviral activity.

Primary Objective: The primary objective is to determine the feasibility and safety of administering CHM-CTLs to mediate antiviral activity in HSCT recipients with viral reactivation or infection. We will closely monitor the effects of these cells on GVHD.

Secondary Objectives: Secondary objectives are to determine: effects of CHM-CTL infusion on viral loads, reconstitution of antiviral immunity, persistence of infused CHM-CTLs and effects on clinical signs of viral infection. In addition, we will estimate the incidence of viral reactivations within 6 months. Additional endpoints include chronic GVHD, clinical response to CTL infusions, effects of HLA matching and overall survival.

Eligibility: Subjects will be eligible following any type of allogeneic transplant if they have CMV, adenovirus or EBV infection persistent despite standard therapy (as defined). If subjects are receiving steroids for treatment of GVHD or for other reasons, dosage must have been tapered to <0.5mg/kg Prednisone (or equivalent) prior to study enrollment. Subjects may not have received ATG, or Campath or other immunosuppressive monoclonal antibodies in the last 28 days. Subjects must have an absolute neutrophil count (ANC) greater than 500/ μ L with no active acute GVHD grades II-IV.

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