Persistent Cytomegalovirus Retinitis following Hematopoietic Stem Cell Transplantation Treated with Viral-Specific T Cells

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Abstract

Cytomegalovirus retinitis (CMVR) following hematopoietic stem cell transplantation (HCT) for a primary immunodeficiency is a rare but highly morbid condition with potential irreversible consequences despite optimal antiviral pharmacotherapy. Viral-specific T cells (VSTs) pose a promising and safe approach eradicating intractable viral disease. We describe the case of a 21-month-old male with Wiskott-Aldrich syndrome (WAS) and CMVR post-HCT with sustained long-term virologic and clinical response after CMV-specific T cell therapy. This case highlights the need to consider VSTs as an adjunct upfront strategy in refractory CMVR and for routine ophthalmologic screening and surveillance in high-risk patients post-HCT.

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Abbreviations and Acronym Key:

aGvHD	Acute Graft-versus-Host Disease
BK	BK human polyomavirus
CMV	Cytomegalovirus
CMVR	Cytomegalovirus retinitis
EUA	Exam under anesthesia
GCV	Ganciclovir
HCT	Hematopoietic Stem Cell Transplantation
IRU	Immune recovery uveitis
JC	JC human polyomavirus
MRI	Magnetic resonance imaging
PHA	Phytohemagglutinin
PCR	Polymerase chain reaction
VSTs	Viral-specific T cells
WAS	Wiskott-Aldrich Syndrome

Abstract

Cytomegalovirus retinitis (CMVR) following hematopoietic stem cell transplantation

(HCT) for a primary immunodeficiency is a rare but highly morbid condition with potential irreversible consequences despite optimal antiviral pharmacotherapy. Viral-specific T cells (VSTs) pose a promising and safe approach eradicating intractable viral disease. We describe the case of a 21-month-old male with Wiskott-Aldrich syndrome (WAS) and CMVR post-HCT with sustained long-term virologic and clinical response after CMV-specific T cell therapy. This case highlights the need to consider VSTs as an adjunct upfront strategy in refractory CMVR and for routine ophthalmologic screening and surveillance in high-risk patients post-HCT.

Introduction

Wiskott-Aldrich syndrome (WAS) is an X-linked disease caused by mutations in the *WAS* gene leading to thrombocytopenia, eczema, recurrent infections, autoimmune disease, and malignancy[1]. If transplanted prior to 5 years of age, hematopoietic stem cell transplantation (HCT) offers a curative outcome with a survival of >94%[2]. Despite excellent survival outcomes, infections due to delayed immune recovery remain a source of morbidity.

Disseminated CMV viremia post-HCT occurs in 60-85% of patients with CMV seropositive status, especially in the setting of a T cell-depleted graft[3]. CMV retinitis (CMVR) after HCT is rare, but can cause potential devastating visual consequences. The median onset of CMV following HCT is Day +34, and the median time of diagnosis of CMVR is Day+ 251 post-HCT[4,5]. The minimal symptoms in the early stages of CMVR and its suboptimal response to systemic and intra-vitreal antiviral therapy, make CMVR a very challenging condition to diagnose and treat.[4] Recently, virus-specific T lymphocytes (VSTs) have been used to treat systemic CMV, as they were found to be effective in 83% of subjects treated for CMV infection[6].

In this report, we describe the successful case of an infant that received CMV-specific T cells after developing persistent CMV viremia and retinitis following a TCRαβ/CD19 B cell-depleted haploidentical HCT despite

standard antiviral therapy, achieving full donor chimerism, $CD3^+$ T cell recovery (>1000 cells/μL), and normal phytohemagglutinin (PHA)-induced blastogenesis.

Case Report

A 7-month-old Asian male was diagnosed with WAS after he presented with gastrointestinal bleeding and thrombocytopenia with a gene mutation in the WAS gene (WAS 665del, p/Pro222Ginfs). The patient underwent a paternal (CMV+) TCRαβ/CD19 B cell-depleted HCT following conditioning chemotherapy with busulfan, fludarabine, thiotepa, and rituximab. A cell dose of 38 x 10^6 $CD34^+$ cells/kg was infused with an αβ T cell dose of 0.49 x10^5 cells/kg. The patient achieved neutrophil and platelet engraftment on Days +17 and +13, respectively. Donor chimerism was 100% at Day +30 and remained at the same level 2 years post-HCT. Post-HCT complications included maximum grade 2 skin and GI acute graft-versus-host disease (aGvHD), which resolved after a short course of systemic corticosteroids. On routine surveillance, CMV reactivated on Day +49 with a maximum viral load of 53 060 IU/mL occurring on Day +78 (Fig. 1). At the time of CMV reactivation, absolute $CD3^+$ T cells were 65/μL and $CD4^+$ T cells 36/μL. Serial eye exams following CMV diagnosis were unremarkable. He received induction dosing with foscarnet followed by treatment dosing with ganciclovir (GCV). Of note, CMV resistance testing was negative.

On Day +158, he presented with a 1-week history of rotary bilateral nystagmus and a CMV viral load of 520 IU/mL. $CD3^+$ T cells were 1 488/μL and $CD4^+$ T cells were 233/μL. Brain MRI showed right optic nerve enhancement (Fig. 2A) and an exam under anesthesia (EUA) revealed bilateral granular CMVR with retinal vasculitis and severe cystoid macular edema concerning for concomitant immune recovery uveitis (IRU) (Fig. 2B). The aqueous humor was positive for CMV bilaterally. The patient received both systemic and intra-vitreal foscarnet and GCV with anterior chamber paracentesis bilaterally. After the second intra-vitreal injection, the aqueous humor was culture-negative for CMV. Systemic and single sub-tenons corticosteroid injections were given to each eye for superimposed IRU.

CMV PCR became undetectable in the blood on Day +216 and the patient's nystagmus improved but did not resolve. An EUA showed improved macular edema and inactive retinitis bilaterally but the patient developed uveitis due to the corticosteroid injections, for which IV tocilizumab for a total of 4 monthly doses was provided. Surveillance EUA on Day +295 showed recurrent CMVR in the right eye despite negative CMV serum titers in both blood and aqueous humor (Fig. 1). $CD3^+$T cells were 94/μL and $CD4^+$ T cells were 30/μL, which was attributed to tocilizumab since T cell engraftment remained 100%.

The patient was subsequently enrolled on a phase II clinical trial (NCT02532452) for the use of third-party quadrivalent VSTs[7]. The patient, then 21-months-old, received 3 doses of CMV-specific T cells over 3.5 months spaced 4-6 weeks apart. Following the first dose, $CD3^+$ T cells increased from 994/μL to 3 372/μL and $CD4^+$ T cells increased from 284/μL to 1 389/μL. After the third infusion, retinitis resolved and both the aqueous humor and blood remained negative for CMV. As of this manuscript's submission date, the patient is 11-months post the first infusion of CMV-specific T cells, remains without evidence of CMVR, has normal immune reconstitution ($CD3^+$ T cells 3 440/μL; $CD4^+$ T cells 1 583/μL) and a normal mitogen stimulation test (PHA).

Discussion

Despite the curative potential of HCT for patients with WAS, post HCT infectious complications such as disseminated CMV infection occur in 60-85% of patients with CMV seropositive status, especially in the setting of a T cell depleted graft[8]. CMVR, occurring in up to 5.6% of cases, can be visually devastating[9].

This case highlights the importance of thorough and regular examinations of the eyes in patients with CMV viremia. Although this particular patient had early examinations that did not detect CMVR, it is important to continue long-term monitoring if CMV is refractory.

HCT graft manipulation strategies such as TCRαβ/CD19-depletion significantly mitigate the risk of aGvHD, which is important for non-malignant diseases such as WAS[10]. However, the consequent delay in immune reconstitution increases the risk of opportunistic infections as B cell and $CD8^+$ T cell numbers don't normalize

until 100-180 days and thymic-dependent $CD4^+$ T cells until 6-9 months post-HCT[11]. The risk of viremia for CMV seropositive HCT recipients is inversely correlated with the frequency of graft-derived CMV-specific T cells and the timing of CMV-specific T cell immune reconstitution after HCT[12]. In this patient, the rapid increase in $CD4^+$ T cells following VST infusion was key to CMVR resolution.

Although CMVR improves in the majority of affected patients[13], this patient had persistent CMVR despite months of intravitreal and systemic antiviral therapy, negative resistance testing, and a reconstituting immune system. The adoptive transfer of VSTs offers a promising alternative to conventional therapy in treating viral infections such as CMV, adenovirus, BK, and JC virus[3,14,15]. Studies have shown resolution of CMV viremia after one to two doses of VSTs in approximately 85% of patients[16]. Gupta et al. treated seven patients, aged 26-68 years, who had CMVR with VST with a 90% resolution of the disease with a median follow-up of 33 months[17]. Additionally, there is one case report of a 3-year-old who also achieved remission of CMVR following VSTs[18]. Our patient was 21 months of age at the time of CMV-specific T cell infusion.

There are many advantages for using VST early, especially for young children. First, serial intra-vitreal injections of foscarnet and GCV require frequent examinations under anesthesia. Repeat episodes of general anesthesia have been correlated with an increased risk of neurodevelopmental delay[19]. Second, intra-vitreal injections carry risk of systemic and ocular morbidity, including endophthalmitis, intraocular inflammation, retinal detachment and intraocular pressure elevation. Any of these can result in permanent vision loss[17,20].

In conclusion, ongoing ophthalmologic evaluations of children with persistent CMV viremia are needed to detect CMVR early. Initiation of treatment with CMV-specific T cells should be considered early for the treatment of patients with CMVR as an adjunct therapy in children who have resistant CMV disease.

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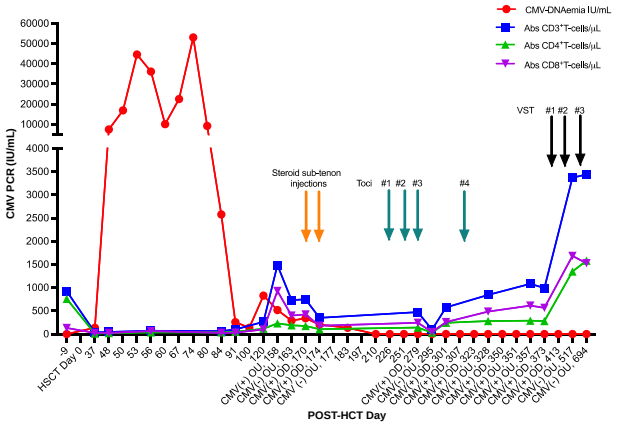
Figure and legend list:

Figure 1. CMV DNA plasma titers by PCR (y-axis) and therapeutic interventions throughout HSCT course over time (x-axis). Exams under anesthesia (EUA) are indicated as well as CMVR status based on qualitative CMV DNAemia results in aqueous humor of right (OD) and left eye (OS), respectively.

Figure 2. A) MRI Brain on day of CMVR recurrence (Day +158 post-HCT) showing right optic nerve enhancement. B) Composite of Fluorescein Angiography (FA), Color Fundus Photography (CFP), and Optical Coherence Tomography B-scans (OCT) of right (OD) and left eye (OS), respectively. Grey panels indicate no imaging from the patient was collected on that date. Panels A-F: imaging from initial exam under anesthesia (Day +158 post-HCT). Panels G-J: imaging from time of quiescence prior to initiation of tocilizumab (Day +226 post-HCT). Panels K-N: imaging from 6 months after final tocilizumab infusion and 2 rounds of VST therapy (Day +517 post-HCT). Panels S-X: imaging from most recent EUA with quiescence and improvement after 3 rounds of VST therapy (Day +694 post-HCT). Yellow arrows show progressive decrease in optic disc edema and retinal vasculitis (represented by decreased hyperfluorescence in angiogram) and red arrows show progressive decrease in macular edema (represented by decreased retinal thickening on OCT) in both eyes.



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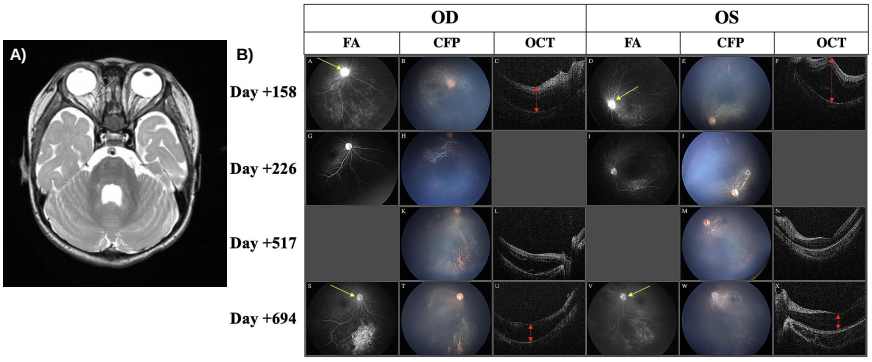

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