Rapid Salvage Treatment With Virus-Specific T Cells for Therapy-Resistant Disease

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Background. Viral infections are major complications after allogeneic hematopoietic stem cell transplantation (HSCT). During posttransplant immunosuppression the regular T-cell control is compromised. Even if treatment strategies against infections caused by herpes viruses such as cytomegalovirus, Epstein-Barr virus, and adenovirus have improved, the mortality rate is still considerable. If primary antiviral therapy fails or cannot be tolerated, adoptive therapy with virus-specific cytotoxic T cells (CTL) can be utilized.

Methods. In this study, we used virus-specific CTLs to treat 8 patients suffering from severe viral infections after allogeneic HSCT. Using positive selection with HLA multimers and magnetic beads, we isolated CTLs from both frozen donor material as well as third-party donors within hours.

Results. At 90 days after CTL infusions 7 out of 8 patients were still living. CTLs infused from third-party donors were detected in 5 of 6 patients up to 76 days after infusion. No graft-versus-host disease associated with CTL infusions was observed.

Conclusions. Our separation approach offers a rapid alternative for adoptive CTL therapy if primary antiviral treatment strategies fail. Because no prolonged expansion steps are needed, this method may be used for early treatment of patients suffering from life-threatening infectious complications.
this is followed by rituximab (anti-CD20 monoclonal antibody). In most patients, the presence of CMV DNA in plasma is successfully treated with ganciclovir or foscarnet [11]. In some patients with adenovirus infection, cidofovir may have a controlling effect [12]. However, in severely immunocompromised allogeneic HSCT patients, repeated courses of antiviral therapy are often necessary because they will increase the development of drug-resistant virus strains, although the overall mortality from drug-resistant viremia after HSCT is still considerable [3, 13].

Another treatment approach is to enhance the virus-specific CTL response by adoptive transfer of virus-specific CTLs from the donor. In 2002 Einsele et al showed this approach to be successful for resistant CMV disease after allogeneic HSCT [14]. Despite a high efficacy of the standard method of adoptive T-cell immunotherapy, the procedure is laborious and time consuming and it is often too late to administer the procedure to the patient [14–17]. In addition, after, for example, cord blood transplantation, a donor is not available. We and others have recently developed new methods for treating life-threatening viral diseases where virus-specific T cells are selected ex vivo and directly infused into the patient. By excluding cumbersome expansion steps in vitro, these methods may be used to treat patients within days instead of weeks [18–20]. In this study we implemented this new approach for treating difficult-to-treat viral infections (CMV, EBV, and adenovirus) in transplant recipients as well as infants with active infection before transplantation.

MATERIALS AND METHODS

Patients

Eight patients, 5 males and 3 females, were included in the study due to insufficient treatment response to conventional antiviral treatment or drug-related toxicity. The study was approved by the regional ethical committee in Stockholm. Seven patients underwent HSCT between 2009 and 2011. The eighth patient was an infant with severe combined immunodeficiency (SCID) treated prior to HSCT to control a severe CMV infection. Patient characteristics are listed in Table 1.

Flow Cytometry Staining

Peripheral blood mononuclear cells (PBMCs) were washed in phosphate-buffered saline (PBS) and stained with the negative control SLYNTVATL pentamer or with the relevant HLA-pentamers from ProImmune Ltd. (Oxford, UK) for 20 minutes at room temperature. The cells were then washed in PBS and stained with CD3 (UCHT1) and CD8 (RPA-T8)-specific antibodies from BD Bioscience (San Jose, CA) on ice and analyzed on a fluorescence-activated cell-sorting analyzer using CellQuest software (BD Labware, Franklin Lakes, NJ).
CTL Preparation

When whole blood was used as the source for CTL preparation, 450 mL was drawn from the donor into a CPD/SAG-M quadruple-bag blood container system (Fenwal, La Châtre, France) [21]. The blood from the donor was then either diluted 1:1 with CliniMACS PBS/ethylenediaminetetraacetic acid (EDTA) buffer (Miltenyi Biotec GmbH, Bergisch-Gladbach, Germany) and PBMCs separated using density-gradient centrifugation (Lymphoprep, Fresenius Kabi Norge AS) or separated on a Ficoll gradient on the Cobe Spectra, before washing in CliniMACS PBS/EDTA buffer 4 times. If frozen graft material was available, cells were thawed and washed in CliniMACS PBS/EDTA buffer twice. Cells were then stained with relevant allophycocyanin (APC)-labeled peptide-containing HLA pentamer for 30 minutes followed by a secondary incubation with anti-APC magnetic beads (Miltenyi Biotec GmbH) for 20 minutes on ice. After washing, cells were run through LS columns (Miltenyi Biotec GmbH). The positive fraction, which consisted of pentamer-positive cells, was eluted, washed, and analyzed for purity by flow cytometry (Table 2). Cells were then diluted in saline solution with 10% human AB serum and injected intravenously.

Chimerism Analysis

Using short-tandem repeats as polymorphic markers, chimerism analysis was performed to distinguish HSCT donor, recipient, and CTL donor [22]. After polymerase chain reaction (PCR) amplification, the products were analyzed with capillary electrophoresis on a 3130 genetic analyzer (Applied Biosystems, Foster City, CA).

Viral Quantification

Quantification of the presence of CMV DNA in plasma was performed on whole blood samples using a real-time PCR method [23]. For EBV, a slight modification of a previously described real-time PCR assay for serum was used to quantify DNA [24]. Regarding adenoviral DNA, a real-time PCR assay measuring the hexon gene in plasma or serum was used [25].

RESULTS

CMV-Specific T Cells Can Be Separated From Frozen Donor Material and Used for Adoptive Therapy

Donor lymphocyte infusions (DLIs) after transplantation have successfully been reported to have a positive effect on certain malignant relapses after HSCT [26, 27]. Because of this, residual graft material is frozen and saved. DLI has also been used to treat post-HSCT infections. Due to the risk of GVHD, a selection of specific T cells from the DLI is warranted [28]. Two male patients with the presence of CMV DNA in plasma who were unresponsive to antiviral therapy were treated with
CMV-specific T cells separated from frozen DLI material (Figure 1).

Patient CMV 1 was initially treated with ganciclovir to treat CMV reactivation and viremia 25 days post-HSCT. Due to renal insufficiency, treatment was discontinued on day 29 but restarted using lower doses on day 34 when the patient had high viral copies (568,000 copies/mL). Despite ganciclovir treatment, viral copies continued to increase, and the decision was made to infuse virus-specific T cells extracted from frozen DLI. The patient was under continuous immunosuppression before and after T-cell infusion. No CMV-specific T cells against the HLA-A2-restricted pp65 peptide NLVPV ATM were detected in the patient preinfusion (Figure 1A). T cells were infused on day 44. On day 70, virus was no longer detected in blood and the frequency of epitope-specific T cells had reached 3% with the use of staining with the HLA-A2-restricted peptide NLVPV ATM pentamer.

In patient CMV 2 the situation was analogous. Ganciclovir was discontinued due to cerebral toxicity with confusion on day 36. Foscarnet was also tried starting on day 71. The decision was made to administer specific T cells on day 72. Specific cells against the CMV-derived peptide NLV were detected in the patient preinfusion (Figure 1A). T cells were infused on day 44. On day 70, virus was no longer detected in blood and the frequency of epitope-specific T cells had reached 3% with the use of staining with the HLA-A2-restricted peptide NLVPV ATM pentamer.

CMV-Specific T Cells From Haplo-Identical Relatives Can Be Used as Treatment in Allogeneic Transplanted Patients

After cord blood transplantation or when no additional donor material is available, a third-party donor of virus-specific T cells can be an alternative for treatment of fulminate viral diseases post-HSCT [29, 30]. In 3 patients with active CMV infection unresponsive to antiviral therapy, T cells against the HLA-B7-restricted TPRVTGGGAM peptide (Figure 2A), HLA-A2-restricted NLVPV ATM peptide (Figure 2B), or B35-restricted HPVGEADYFEY peptide (Figure 2C) were infused.

Patient CMV 3 had reactivation of CMV 25 days post-HSCT. She was on foscarnet days 25–43 and ganciclovir was added on day 61. She remained positive for CMV in blood, and the decision was made to administer CTL from her mother, which she received on day 80. Two weeks postinfusion she had detectable TPR-specific T cells in blood. The CMV-specific T cells were separated, and a chimerism assay was performed in order to determine the origin of the virus-specific T cells. We confirmed that 75% of the specific T cells were from the CTL donor (Figure 2A). The patient had no detectable viral copies in blood 28 days post-CTL infusion.

Patient CMV 4 had reactivation of CMV 20 days post-HSCT with low, fluctuating titers that ranged from 1000 to 3000 copies over 30 days. Ganciclovir was tolerated but failed to clear the viremia. Although no CD3+ cells were detected (data not shown) on day 35, the decision was made to infuse

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**Figure 1.** Cytomegalovirus (CMV)–specific T cells for adoptive therapy can be prepared from frozen donor material. Frozen donor lymphocyte infusions (DLIs) were thawed and washed before positive selection of cells labeled with NLV-containing HLA-A02 pentamers. On the left, frequencies of pentamer+ CD8+ T cells in cytotoxic T lymphocyte (CTL) donors and patients before and after CTL infusion are shown for CMV (A) patient 1 and (B) patient 2. Fraction of CD8+ T cells in total peripheral blood mononuclear cells is indicated below each patient fluorescence-activated cell-sorting plot. To the right, CMV titers are plotted against days posttransplantation for both patients. A dashed vertical line designates the day of CTL infusion. Abbreviations: CMV, cytomegalovirus; CTL, cytotoxic T lymphocyte; pat, patient.
specific T cells from the patient's daughter. Peripheral blood samples from up to 8 weeks after T-cell infusion failed to show any T cells with the same peptide specificity as the infused cells. Chimerism analysis of the total CD3+ population showed only the presence of the original HSCT donor (Figure 2B). The patient continued to have detectable viral copies in blood until >90 days after CTL infusion.

Patient CMV 5 had reactivation of CMV on day 27 post-HSCT. He was started on foscarnet, with good initial response, although it was discontinued due to hemorrhagic cystitis. The patient was changed to ganciclovir; however, due to remaining viral copies, the decision was made to infuse specific T cells from his haplo-identical brother on day 80 post-HSCT. His immune suppression did not change during the entire period. Twelve weeks post-CTL infusion, specific T cells from the brother remained detectable by chimerism analysis (Figure 2C). No viremia was detected 20 days after CTL transfusion.
CMV-Specific T Cells From the Mother Can Be Used to Treat Immune-Compromised Neonates

Active CMV disease during the conditioning treatment for HSCT is associated with an exceedingly increased risk of death [31].

Cord blood transplantation was planned for patient CMV 6 due to SCID. The child was started on ganciclovir due to high CMV DNA copy numbers. No effect on CMV DNA levels was observed after 2 weeks of treatment. To decrease the viral load before HSCT, the decision was made to infuse HLA-A2-restricted CMV-specific T cells to fight against the HLA-A2-restricted peptide NLVPVATM. Cells from the mother were isolated and infused on day 7 pretransplantation. The ganciclovir was continued during the entire period. On day 1 pretransplantation-specific T cells against the same epitope were detected in the patient. Chimerism analysis of NLVPVATM-specific T cells revealed that a proportion (approximately 35%) of cells had mother origin. The level of CMV DNA in blood was reduced from 768,000 to 70,000 copies/mL 1 week after infusion (Figure 3). Subsequent to cord blood transplantation, no more monitoring could be performed.

EBV and Adenovirus-Specific T Cells From Haplo-Identical Relatives Can Be Used

EBV and adenovirus infections are additional infectious complications associated with the lymphopenic state postallogeneic HSCT [6, 32, 33].

On day 36 after HSCT, patient adeno 7 developed adenoviral infection with fever and 160,000 viral copies/mL blood. His immunosuppressive treatment was tapered and 5 mg/kg cidofovir was administered intravenously once weekly for 8 weeks. In spite of this, his fever continued and adenoviral copies in blood continued to increase. The decision was made to administer HLA-A1-restricted TDLGNL Argentine adenovirus-specific T cells from his mother. The patient was under low-dose immunosuppression during the entire phase. The patient had nondetectable CD3⁺ T cells before infusion. On day 4 after infusion, a small number of virus-specific T cells were detected transiently. Seven days after infusion, the cells were no longer detectable. With chimerism, virus-specific T cells from the mother were detected at day 3 but not subsequently (Figure 4A). Due to increasing viral copies, virus-specific T cells from the mother were infused a second time 2 weeks later. No specific T cells or CD3⁺ T cells were detected after infusion (data not shown), and the patient later died from the adenoviral infection.

Patient EBV 8 was previously treated with HLA-A2-restricted GLCTLVAML peptide-specific CTLs to fight against EBV lymphoma from her mother. These T cells remained until 76 days after infusion [29]. On day 305 post-HSCT, the patient returned with fever, and EBV was detected in blood, colon, and tonsils. No maternal CTLs were detected. Due to suspected disease progression, the decision was made to once again administer EBV-specific T cells from the mother. This time, T cells with specificity against both GLC and CLG were infused. Her tonsillitis was cured in 2 days, and colon biopsies tested negative for EBV after 1 week. The patient was virus negative in blood 2 weeks postinfusion. With chimerism, infused cells from the mother were detected almost 2 months postinfusion (Figure 4B).

DISCUSSION

Viral infections and disease remain major problems after allogeneic HSCT and, in some cases, lethal [6, 32]. Even though the

![Figure 3](cid201255figures-3.png)
mortality rate caused by CMV substantially decreased after the introduction of preemptive therapy with antiviral drugs such as ganciclovir, therapy-resistant cases still occur [34]. Because the average age of patients undergoing allogeneic HSCT is increasing, there are also larger numbers of individuals who cannot tolerate the relatively toxic characteristics of antiviral drugs.

Many studies have proven the efficacy of anti-viral CTL treatment for CMV, EBV, and adenoviral infections in patients after allogeneic HSCT as well as solid organ transplantation [14, 35, 36]. The majority of these studies focus on cumbersome amplification procedures to increase the specificity of T cells after repeated in vitro expansions. Despite recent advances, the minimum time needed for these protocols is still 18 days, in some cases making them too slow for clinically life-threatening situations [37]. Today, alternative strategies such as interferon-capture methods of virus-specific CTLs as well as allogeneic CTL banks have been tried in order to address this issue [35, 38].

Here we focused on another approach, relying on the infusion of small numbers of directly separated T cells and their potential for subsequent in vivo expansion after infusion into the recipient [29]. The first approach in which a similar strategy was used was described by Cobbold et al [39]; 9 patients with CMV reactivation were treated with cells from the

Figure 4. Epstein-Barr virus (EBV) and adenovirus-specific T cells for adoptive therapy can be prepared from haplo-identical relatives. Peripheral blood mononuclear cells from cytotoxic T lymphocyte (CTL) donor were washed before positive selection of cells labeled with GLCTLVAML- and CLGGLTMV-containing HLA-A02 pentamers or TOLGONLY-containing HLA-A01 pentamers, respectively. (A) For patient 7, the left panel shows fluorescence-activated cell-sorting (FACS) plots for frequencies of pentamer+ T cells in the CTL donor, in the patient before CTL infusion, and 1 and 6 days after CTL infusion. In the middle panel, adenovirus titer are plotted against days after transplantation. The day of CTL infusion is indicated by a dashed vertical line. The right panel shows chimerism patterns of cells from the patient before hematopoietic stem cell transplantation (HSCT), the HSCT donor, the CTL donor, and separated adenovirus-specific T cells from the patient 1 day and 6 days after CTL transfusion. (B) For EBV patient 8, the left panel shows FACS plots for frequencies of GLC- and CLG-positive cells, respectively, in the CTL donor and in the patient before and after CTL infusion. In the middle panel, EBV titers are plotted against days after transplantation. The day of CTL infusion is indicated by a dashed vertical line. The right panel shows chimerism patterns of cells from the patient before transplantation, the HSCT donor, the CTL donor, and separated GLC- and CLG-specific T cells from the patient after CTL infusion. (Figure 4B, right panel. Reproduced with kind permission from Springer Science + Business Media: <Cancer Immunol Immunother. 2010; 59:473–7, Uhlin et al, fig.1.e>). Abbreviations: CTL, cytotoxic T lymphocyte; EBV, Epstein-Barr virus; HSCT, hematopoietic stem cell transplantation; pat, patient.
original HSCT donor. Recently, Schmitt et al reported on 2 cases treated with streptamer-selected CMV-specific CTLs [20]. The need for rapid measurements is accomplished with this approach, and CTL therapy can be successfully implemented not only for preemptive measures but also to treat individuals with life-threatening symptoms. This treatment strategy can easily be adopted as a complement to standard viral therapy by smaller clinics without a considerable economic burden. In addition, it is favorable that the separation can be performed using only 400 mL of whole blood, which is in contrast to leukopheresis, making the procedure safe and uncomplicated for the donor.

In this study we treated 8 patients with infections caused by 3 diverse viruses and different clinical histories with a similar procedure. We showed that the method is robust and can be an alternative for patients in life-threatening situations. In these types of clinical situations, it is often hard to prove the true efficacy of infused T cells due to additional treatment strategies, changes in immunosuppression, and natural clearance of the infections [29, 30, 38]. In this study we show strong circumstantial evidence, with residing infused virus-specific T cells detected by chimerism in 5 of 6 evaluable patients postinfusion. In addition, 6 of 8 patients showed a decrease in viral titers within 2 weeks post-CTL infusion.

In some cases, such as patient CMV 2, virus-specific T cells were detected before CTL infusion. We could not determine the functionality of these cells, making it difficult to distinguish their effect from that of the infused cells. However, an additional effect can still be speculated.

Despite the small number of patients in this study, 90-day survival for 7 of 8 patients is noteworthy. Although only 4 patients were living 1 year after infusion, none had additional problems due to the original viral disease. However, the fact that 4 patients died for other reasons 1 year later emphasizes the need for preemptive rather than therapeutic use of immune therapy postallogeneic HSCT.

For EBV-related PTLD, several researchers have identified risk factors after allogeneic HSCT [6, 13, 33]. Preemptive therapy with rituximab has been extensively used to inhibit viral EBV reactivation and to prevent or treat PTLD [40, 41]. This is also true for the use of antiviral drugs as preemptive treatment for CMV and adenovirus infections [12, 42]. Theoretically, this approach should be possible for all patients undergoing allogeneic HSCT with risk factors for any of the 3 viruses—EBV, CMV, and adenovirus infections.

In a majority of HSCT patients, adoptively transferred T cells are needed during the phase when immunosuppression occurs. Because of this, the approach that uses haplo-identical T cells is attractive. Putatively, the MHC-mismatched T cells will, due to the immunosuppressed milieu, remain to transiently fight the pathogen, allowing the individual’s new immune system to recover and take over. When the patient becomes immune competent, the haplo-identical T cells will be rejected. This is in agreement with our observation that only transient detection of T cells is possible in most patients.

There is an underlying risk that the infused CTL’s function is impaired by ongoing immunosuppression. Tacrolimus (FK506) and cyclosporin inhibit both the proliferation and function of CTLs [43]. To address this, several groups have investigated the possibility of engineering ex vivo–generated virus-specific CTLs that are resistant to calcineurin inhibitors [44, 45]. Our approach could benefit from this additional strategy because some of our patients remained under immunosuppression.

The differentiation status of the infused T cells could not be determined from this study. Studies have indicated that the in vivo longevity of infused T cells can be partly dependent on the memory profile [46]. In addition, recent data have also demonstrated a memory T-cell subset with stem cell–like features [47]. With this in mind, preanalysis of differentiation parameters like this on the infusion product might be helpful in both predicting the outcome of adoptive T-cell transfer as well as in choosing the optimal donor.

In conclusion, the separation approach described here offers a cheap and quick alternative for separation and adoptive CTL therapy if primary treatment strategies such as antiviral therapy fail. Because the technique does not involve any prolonged expansion steps in vitro, it can readily be used to treat patients suffering from life-threatening illnesses.

Notes

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