**Transfer of Hexon- and Penton-selected adenovirus-specific T cells for refractory adenovirus infection after haploidentical stem cell transplantation**

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**Abstract**
Adenovirus (HAdV) infections confer a high risk of morbidity and mortality for immunocompromised patients after stem cell transplantation (SCT). Treatment with standard antiviral drugs is of limited efficacy and associated with a high rate of adverse effects. HAdV-specific T cells are crucial for sustained viral elimination and the efficacy of adoptive T-cell therapy with donor-derived HAdV-specific T cells has been reported by several investigators. Here, we report our experience with the transfer of HAdV-specific T cells specific for penton, which was recently identified as an immunodominant target of T cells, and hexon in a 14-year-old boy after T-cell-depleted haploidentical SCT for myelodysplastic syndrome (MDS). He developed severe HAdV-associated enteritis complicated by acute graft-versus-host disease (GvHD). The patient received ten infusions of allogeneic HAdV-specific T cells manufactured from the haploidentical stem cell donor using the Clinimacs Interferon-γ (IFN-γ) cytokine capture and immunomagnetic selection. Initially, T cells were generated against the immunodominant target hexon and in subsequent transfers dual antigen-specific T cells against hexon and penton were applied. T-cell transfers were scheduled individually tailored to current immunosuppressive treatment. Each transfer was followed by reduction of HAdV load in peripheral blood and clinical improvement. Importantly, T-cell responses to both penton and hexon pools emerged in patient blood after repetitive transfers. Unfortunately, the patient experienced bacterial sepsis, and in this context, severe GvHD requiring intensive immunosuppression followed by secondary progression of HAdV infection. The patient succumbed to multiorgan failure 283 days after SCT. This case demonstrates the feasibility of HAdV-specific T-cell transfer even in the presence of immunosuppressive treatment. Targeting of multiple immunodominant viral proteins may prove valuable in patients with complicated HAdV infections.

Schultze-Florey, Tischer-Zimmermann, Eiz-Vesper and Maecker-Kolhoff contributed equally to the manuscript.

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1 | CASE PRESENTATION

A 14-year-old boy suffered from Shwachman-Bodian-Diamond syndrome and developed a myelodysplastic syndrome (refractory cytopenia) with monosomy 7. In the absence of a matched related or unrelated donor, he underwent haploidentical SCT. After myeloablative conditioning with upfront CCE (clofarabine $[1 \times 40 \text{mg/m}^2, \text{day } -18 \text{ to } -16], \text{cyclophosphamide } [1 \times 400 \text{mg/m}^2, \text{day } -18 \text{ to } -16], \text{etoposide } [1 \times 100 \text{mg/m}^2, \text{day } -18 \text{ to } -16]) \text{ followed by fludarabine } [1 \times 40 \text{mg/m}^2, \text{day } -8 \text{ to } -5], \text{thiotepa } [2 \times 5 \text{mg/kg, day } -4], \text{melphalan } [1 \times 70 \text{mg/m}^2, \text{day } -3 \text{ to } -2], \text{ATG } [1 \times 1 \text{mg/kg, day } -12; 1 \times 9 \text{mg/kg, day } -11 \text{ to } -10; 1 \times 10 \text{mg/kg, day } -9]), \text{he underwent SCT with a TCRαβ/CD34+ cells (11.5} \times \text{10}^{5}/\text{kg CD34+ cells, } 18.2 \times \text{10}^{6}/\text{kg TCRαβ+ cells, } 13.8 \times \text{10}^{5}/\text{kg CD34+ cells)} \text{from his haploidentical mother. For post-transplant graft-versus-host disease (GvHD) prophylaxis, mycophenolate mofetil (MMF) was used. Neutrophil engraftment occurred on day 15. Acute GvHD grade III of the skin developed on day 19 and responded quickly to systemic steroid treatment. The patient was discharged on day 36. Two months after transplantation, the patient was re-admitted to the hospital with gastrointestinal symptoms (loss of appetite and vomiting). Adenovirus (HAdV species C, type C2) was detected by quantitative PCR in blood (day 72; Figure 1A). Initial treatment with cidofovir did not result in a sufficient response with an increasing viral load from $10^6$ to $10^7$ copies/mL (day 110) in blood and up to $10^9$ copies/mL in stool. Therefore, we decided to switch the therapy to brincidofovir (CMX001) in combination with ribavirin. Upper and lower endoscopy showed no macroscopic or histological evidence of GvHD, thus MMF was discontinued on day 110 after transplantation. Due to a complete lack of lymphocyte reconstitution and persistent high HAdV load, we decided to apply HAdV-specific T cells retrieved from the original stem cell donor. Four subsequent T-cell preparations were manufactured on a CliniMACS Plus device (Miltenyi Biotech) using the IFN-γ cytokine capture system (CCS, Miltenyi Biotech) according to standard procedures. GMP PepTivator AdV5 Hexon was used for the first two preparations. Because of failure to achieve durable response in the patient (Figure 1B) and the presence of penton-directed HAdV-specific T cells in the blood of the mother (Figure 2A,B; Table S1), we decided to include the newly identified immunogenic PepTivator AdV5 Penton for the third and fourth preparation. The child received a total of ten doses of HAdV-specific T cells within a period of 5 months (Table 1, Figure 1A). The first five doses were hexon-selected HAdV-specific T cells. The last five doses were penton- and hexon-selected HAdV-specific T cells between $1.6 \times 10^3$ HAdV-CTLs (cytotoxic T-lymphocytes, CTLs)/kg body weight and $1 \times 10^4$ HAdV-CTLs/kg body weight. The first two doses of T cells were freshly transferred, whereas the others were cryopreserved.

A decrease in HAdV load was seen after the first application of $2.5 \times 10^3$ HAdV-CTLs/kg body weight on day 114 and the concurrent antiviral drug therapy. The blood HAdV load decreased from $5.2 \times 10^9$ to $9 \times 10^4$ copies/mL on day 117. Subsequently, the patient developed a skin rash and worsening diarrhea 2 weeks after cessation of MMF (day 119). Histologically grade I-II skin and duodenal mucosa GvHD were documented and treated with steroids and MMF (Figure 1B). To conserve anti-HAdV effect and avoid GvHD progression, the patient received subsequently lower doses of HAdV-CTLs ($5 \times 10^3 \text{HAdV-CTLs/kg body weight}$) in short intervals every other week and finally weekly (Table 1). Due to poorly responsive GvHD, immunosuppression was then changed on day 150 to ruxolitinib, prednisolone, and extracorporeal photopheresis on two subsequent days every two. To improve cellular reconstitution, the boy received a CD34-selected stem cell boost (day 188) from his haploidentical mother ($1.7 \times 10^3 \text{CD3+ T cells/kg body weight}$). Diarrhea still persisted, and brincidofovir was discontinued for severe hyperbilirubinemia (day 189). However, GvHD of the liver was observed histologically. Sirolimus was introduced instead of ruxolitinib to enhance virus-specific effector function while preserving GvHD treatment (day 216). To further improve the antiviral effects of CTL therapy, a subsequent HAdV-specific T-cell product consisting of the penton peptide pool in addition was manufactured as a second stimulus after confirming a strong penton-specific T-cell response in the T-cell donor (Figure 2A,B). He received the first dose of penton/hexon-selected HAdV-specific T cells on day 198 (Table 1). Subsequently diarrhea improved continuously. The viral load decreased from $10^7$ to a minimum of $10^5$ copies/mL. Leukocyte counts ranged between 1000 and 2000/µL containing 100-300/µL lymphocytes. We prospectively measured the HAdV hexon- and HAdV penton-specific T-cells via ELISpot from day 103 on. A response for hexon-selected HAdV-specific T cells was detected after eight transfusions (day 225) followed by a response for penton-selected HAdV-specific T cells after ten transfers (day 240; Figure 1B). HAdV-reactive T cells were detectable directly ex vivo and proliferated after in vitro restimulation and 7-day culture.

Unfortunately, the patient developed a bacterial sepsis with multiorgan failure and required subsequent circulation support as well as mechanical ventilation and dialysis (day 248). Immunosuppression was tapered followed by reactivation of the intestinal GvHD. Retreatment with steroids led to a recurrence of HAdV in blood ($10^6$ copies/mL), stool, and bronchoalveolar lavage. Finally, the patient died of multiorgan failure 7 months after the first onset of adenovirus infection and 9 months after stem cell transplantation (day 283).

2 | MATERIAL AND METHODS

Manufacturing of HAdV-specific T cells was carried out with the CliniMACS Plus device and the MACS GMP PepTivator®.
AdV5_Hexon (1st and 2nd manufacturing process) and MACS GMP PepTivator AdV5_Hexon+ MACS research grade PepTivator AdV5_Penton (3rd and 4th manufacturing process) for antigenic restimulation. The intentional use of non-clinical grade PepTivator AdV5_Penton was subjected to and justified by thorough clinical risk-benefit assessment and effective pharmaceutical risk mitigation, parents, and patient were fully informed and provided consent.

Enrichment of IFN-γ-secreting cells was performed by immunomagnetic separation by antibody-conjugated super-paramagnetic particles (CliniMACS IFN-γ Enrichment Reagent, Miltenyi Biotec). Target and non-target cells were quantified by a newly developed single-platform assessment and gating strategy using positive (CD3/CD4/CD8/CD45/IFN-γ), negative (CD14/CD19/CD56), and dead cell (7-AAD) discriminators. The final T-cell products had a mean viability of 53.8% (52.9%-55.0%) in which a mean of 25.5% (19.0%-35.2%) was AdV-specific IFN-γ-positive T cells. For cryopreservation, the eluate fraction was adjusted to 2.86% HSA, 7.5% DMSO (dimethyl sulfoxide), aliquoted, subsequently processed in a controlled-rate freezer, and finally transferred to −140°C or lower in the vapor phase above liquid nitrogen for long-term storage. A fully automated microbial detection system was used for microbiological testing (sterility) of the leukapheresis and the ClinimACS CCS T-cell fraction. Quality control (QC) of the cryopreserved T-cell products (1st process, n = 0; 2nd process, n = 3, 3 × 20 mL, transfused
SCHULTZE-FLOREY ET AL.

Monitoring of HAdV viral load in blood and stool was performed by routine quantitative PCR as described earlier.\(^3\) Quantification of HAdV-specific T-cell frequencies was done before and after T-cell transfer by IFN-\(\gamma\) ELISpot assay as described and using the following peptide pools: ppADV5 Hexon, ppADV5 Penton (all Miltenyi Biotec).\(^1\) If suitable numbers of PBMCs were obtained, HAdV-specific T cells were expanded over 7 days using the respective antigens ppADV5 Hexon and ppADV5 Penton in TexMACS media (Miltenyi Biotec) containing 50 U/mL IL-2 (Peprotec). After 7 days, IFN-\(\gamma\) ELISpot assay was repeated using the respective antigens.

### TABLE 1

| Infusion No. | Production No. | Day | Antigens used for manufacturing | HAdV-CTLs (CD3+)/kg body weight | % IFN-\(\gamma^+\)/CD3+ |
|--------------|----------------|-----|---------------------------------|---------------------------------|-----------------------|
| 1            | 1              | 114 | H                               | \(2.5 \times 10^4\)            | 23.7                  |
| 2            | 2              | 162 | H                               | \(5 \times 10^3\)              | 24.2                  |
| 3            | 2              | 176 | H                               | \(9 \times 10^3\)              | 24.2                  |
| 4            | 2              | 183 | H                               | \(9 \times 10^3\)              | 24.2                  |
| 5            | 2              | 190 | H                               | \(9 \times 10^3\)              | 24.2                  |
| 6            | 3              | 198 | H + P                           | \(1 \times 10^4\)              | 19.0                  |
| 7            | 3              | 204 | H + P                           | \(3.6 \times 10^3\)            | 19.0                  |
| 8            | 3              | 211 | H + P                           | \(3.6 \times 10^3\)            | 19.0                  |
| 9            | 3              | 226 | H + P                           | \(3.6 \times 10^3\)            | 19.0                  |
| 10           | 4              | 239 | H + P                           | \(5 \times 10^3\)              | 35.2                  |

Note: H = PepTivator AdV5 Hexon; P = PepTivator AdV5 Penton.

3: 3rd process, \(n = 4\), \(4 \times 15\) mL, transfused 4; 4th process, \(n = 4\), \(4 \times 20\) mL, transfused 1) was performed as described.
TABLE 2  Overview of clinical studies using HAdV- and multivirus-specific T cells for transfer in chronological order

| Reference          | No. of patients with HAdV infection | Symptoms                                      | T-cell donor | Target specificity (HAdV) | Manufacturing | Doses                  | Time lines | Additional therapies (anti-viral drugs) | Outcome |
|--------------------|-------------------------------------|-----------------------------------------------|--------------|---------------------------|---------------|-------------------------|------------|----------------------------------------|----------|
| Feuchtinger et al16 | 9                                   | Multiorgan: gastrointestinal tract, lung, liver, heart, brain, retina, kidney | Stem cell donor | HAdV lysate | IFN-γ cytokine capture system | 1.2-50 × 10^7 cells/kg body weight (BW) | Therapeutic | Cidofovir, ribavirin, valacyclovir, ganciclovir | 4/9 CR 3/9 NR 1/9 NE |
| Uhlin et al23      | 1                                   | Viremia                                       | Third party family donor | HAdV peptide | Direct isolation via peptide-HLA multimers | 3.1 × 10^6-1.7 × 10^7 cells/kgBW | Preemptive | Cidofovir | 1/1 NR |
| Qasim et al9       | 5                                   | Viremia organ: lung                           | Stem cell donor or third party family donor | HAdV lysate | IFN-γ cytokine capture system + expansion | 1 × 10^4-1 × 10^5 cells/kgBW | Therapeutic | Cidofovir, ribavirin | 3/5 CR 2/5 NR |
| Geyeregger et al24 | 2                                   | Viremia, gastrointestinal and urinary tract, liver | Stem cell donor or third party donor | AdV5 PepTivator (Hexon) | In vitro stimulation and expansion 1x | 1 × 10^4 cells/kgBW | Therapeutic | Cidofovir, ribavirin | 2/2 CR 1/2 survived |
| Feucht et al7      | 30                                  | Nasopharyngeal, gastrointestinal and urinary tract, lung, kidney, liver, brain | Stem cell donor | Hexon protein | IFN-γ cytokine capture system | 5 × 10^7 cells/kgBW (HLA mismatch), 2.5 × 10^6 cells/kgBW (HLA-matched) | Therapeutic | Cidofovir, ribavirin | 18/30 CR 3/30 PR 8/30 NR |
| Qian et al25       | 11                                  | Viremia, gastrointestinal tract, lung         | Stem cell donor or third party family donor | AdV5 PepTivator (Hexon) | IFN-γ cytokine capture system | 5.83 ± 8.23 × 10^7 cells/kgBW | Therapeutic | Cidofovir, ribavirin | 9/11 CR 2/11 NR |
| Withers et al26    | 1                                   | Not specified                                 | Third party donor | AdV5 PepTivator (Hexon) | In vitro stimulation and expansion | 2 × 10^7 cells/m^2 | Therapeutic | Cidofovir | 1/1 CR |
| Ip et al13         | 8                                   | Viremia, gastrointestinal tract               | Stem cell donor | AdV5 PepTivator (Hexon) | In vitro stimulation and expansion | 1 × 10^4-1 × 10^5 cells/kgBW | Preemptive | Cidofovir | 8/8 CR |
| Kallay et al27     | 1                                   | Viremia, gastrointestinal and urinary tract   | Third party donor (family and unrelated) | AdV5 PepTivator (Hexon) | IFN-γ cytokine capture system | 2.7 × 10^6 cells/kgBW | Therapeutic | Cidofovir, foscarnet | 1/1 CR, but died of aspergilosis |
| Gössling et al28   | 1                                   | Viremia, gastrointestinal tract               | Third party donor (unrelated) | AdV5 PepTivator (Hexon) | IFN-γ cytokine capture system | 2.6 × 10^7 cells/kgBW | Therapeutic | Cidofovir | 1/1 CR |
| **Multivirus-specific T cells** |            |                                                |              |                           |               |                        |            |                                        |         |
| Leen et al19      | 5                                   | None                                          | Stem cell donor | Ad5f35pp65 vector infected B-LCLs | Ex vivo expansion | 5 × 10^6-1 × 10^8 cells/m^2 | Prophylactic | Not specified | 5/5 CR |
| Leen et al18      | 13                                  | Gastrointestinal tract                        | Stem cell donor | Ad5f35null vector infected B-LCLs | Ex vivo expansion | 5 × 10^6-1.35 × 10^8 cells/m^2 | Prophylactic (n = 12), therapeutic (n = 1) | Cidofovir | 9/9 CR (received as prophylaxis) 2/2 CR (active disease) |

(Continues)
### TABLE 2

| Reference                  | No. of patients with HAdV infection | Symptoms                        | T-cell donor | Target specificity (HAdV) | Doses | Manufacturing | Manufacturing Time lines | Application | Tumor response |
|----------------------------|-----------------------------------|---------------------------------|--------------|---------------------------|-------|---------------|-------------------------|-------------|-----------------|
| Leen et al                 | 18                                | Not specified                   | Stem cell donor (unrelated)     | Ad53505p65 vector       | Up to 2 × 10^7 cells/m^2 | Third party donor           | Ex vivo stimulation and expansion | Therapeutic Cidofovir | 7/17 CR, 7/17 PR, 3/17 NR |
| Gerdemann et al            | 6                                 | Not specified                   | Third party donor (unrelated)   | NTC385 EpH, Penton       | 5 × 10^6 cells/m^2        | Third party donor           | Ex vivo expansion                | Prophylactic Cidofovir, Ganciclovir | 5/5 CR |
| Papadopoulou et al         | 5                                 | Viremia                         | Stem cell donor (unrelated)     | Overlapping peptides for HAdV, Penton | 5 × 10^7 cells/m^2        | Overlapping peptides for HAdV, Penton | Ex vivo expansion                | Therapeutic Cidofovir | 1/1 CR |
| Tzannou et al              | 10                                | Upper respiratory tract, gastro-intestinal, and urinary tract, lung | Third party donor (unrelated)   | Overlapping peptides for HAdV, Penton | 2 × 10^7 cells/m^2        | Overlapping peptides for HAdV, Penton | Ex vivo expansion                | Therapeutic Cidofovir | 7/10 CR, 7/10 PR, 2/10 NR |

Abbreviations: CR, complete response; NE, not evaluated; NR, no response.

DISCUSSION

Complications after hematopoietic SCT are mainly treatment-related toxicity and viral infections. HAdV infection is among the most common viral infections in pediatric patients and confers a high risk of morbidity and mortality. Mounting an anti-HAdV T-cell response is required for viral clearance. The effects of antiviral drugs (eg, cidofovir and ribavirin) are limited and associated with toxicity and delayed immune reconstitution. The adoptive transfer of adenovirus-specific T cells presents an alternative treatment option.

This case describes a 14-year-old boy with a severe adenovirus infection after SCT treated with HAdV-specific T cells from his haploidentical stem cell donor. This is the first report on the feasibility of adeno-reactive T-cells that had been produced using penton-directed manufacturing and subsequently leading to specific T-cell responses upon adoptive transfer. The adenoviral penton protein is a recently described second immunodominant target. Application of penton-specific T cells improved the immune response shown in ELSpot assay and was followed by a 2 log decrease of viral loads. This underlines the importance for an effective defense against adenovirus. Weekly T-cell transfusions resulted in a stable HAdV-specific T-cell count irrespective of absolute CD3+ T-cell numbers, which could be potentially suppressed through constant GvHD treatment. However, subsequent infusion intervals were 3-4 weeks as already described by Feucht et al and due to persisting infection and availability of the cells. Schedules of T-cell administration may need to be adapted to individual patients on the basis of concurrent GvHD, GvHD treatment, tolerability of antiviral drugs, and efficiency.

The management of GvHD treatment in patients with viral infections is always critical. For the physician, it is a fine line to balance on an effective antiviral treatment with potent immune cells and an intensification of immunosuppression to treat the GvHD. Ruxolitinib as a JAK1/2 inhibitor is a new drug to treat corticosteroid-refractory GvHD as shown in a multicenter survey. There are increasing numbers of reports of infectious complications in patients on ruxolitinib treatment. Ruxolitinib influences the cytokine expression, down-regulates regulatory T cells and interferes with dendritic cells and natural killer cells. In the presented case consistent with short-lived therapeutic effect of adoptive T-cell infusions, ruxolitinib abolished any ELISpot signal even the positive control completely demonstrating the potent ability of this compound to suppress T-cell responses. After switch to sirolimus, sustained T-cell reactivity against HAdV became detectable despite continuously low absolute CD3+ counts. This may be explained by beneficial effects of sirolimus selectively on antivirus memory T-cell function. Therefore, the discontinuation of ruxolitinib switch to an alternative immunosuppressive treatment for GvHD should be strongly considered upon viral infections or reactivations.

In summary, we reported on a boy that received HAdV-reactive T cells from a haploidentical stem cell donor that had been manufactured under GMP conditions using the CCS with overlapping peptide pools. The patient showed no infusion-related toxicity and a...
decrease of viral load suggesting feasibility and effectiveness as similarly described in many recent studies (summary in Table 2).7,8,12,28 In addition, we could detect the immune response by ELISpot demonstrating an induction of penton- and hexon-specific T cells in the patient after transfer. Diligent monitoring of GvHD and anti-HAdV immune response enabled personally tailored immunosuppressive and antiviral therapy and led to control of both GvHD and HAdV infection in this patient.

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CONFLICT OF INTEREST

The authors have no relevant conflict of interest to disclose.

AUTHORS CONTRIBUTION

RSF treated the patient, collected, and analyzed the clinical data and wrote the manuscript; STZ performed experiments on donor selection, quality control and immune monitoring, analyzed the data, and wrote the experimental part of the manuscript; HGH performed blood donation for T-cell transfer and was responsible for GMP T-cell product manufacturing; CP was involved in regulatory issues and GMP T-cell product manufacturing; BL treated the patient and revised the manuscript; AH performed viral monitoring; MS and KWS treated the patient; RB supervised the donor selection and GMP T-cell production, BEV performed the T-cell donor selection, supervised the GMP T-cell product manufacturing, and data analysis and writing of the manuscript; BMK treated the patient, supervised data analysis, and preparation of the manuscript; BEV and BMK designed the project and provided overall academic leadership; and all authors reviewed and approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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