

Multicentre Phase I/II application of Adenovirus-Specific T cells in High Risk Paediatric Patients after Allogeneic Stem Cell Transplantation

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ABSTRACT

Background: Adenovirus reactivation can cause significant morbidity and mortality in children after allogeneic stem cell transplant. Antiviral drugs can control viraemia, but viral clearance requires recovery of cell mediated immunity.

Method: This study was an open label phase I/II study to investigate the feasibility of generating donor derived ADV-specific T cells (*Cytovir® ADV, Cell Medica, London*) and to assess the safety of pre-emptive administration of Adenovirus-specific T cells in high-risk paediatric patients after allogeneic HSCT to treat adenoviraemia. Primary safety endpoints included GvHD, and secondary endpoints determined antiviral responses and use of antiviral drugs.

Results: Between January 2013 and May 2016, 92 donors were enrolled for the production of ADV T cells at three UK centres, and 83 products were generated from 72 mobilised peripheral blood harvests and 20 steady state whole blood donations. Eight children received *Cytovir® ADV* T cells after standard therapy and all resolved ADV viraemia between 15-127 days later. Adenovirus-specific T cells were detectable by ELISpot in the peripheral blood of all patients analysed. Serious adverse events included Grade II GvHD, Astrovirus encephalitis and pancreatitis.

Conclusion: The study demonstrates the safety and feasibility of pre-emptively manufacturing peptide pulsed ADV-specific cells for high-risk paediatric patients after transplant and provides early evidence of clinical efficacy.

KEYWORDS

Adenovirus-specific T cells, adoptive immunotherapy, haematopoietic stem cell transplantation

ABBREVIATIONS

ADV – Adenovirus

ATG – polyclonal rabbit thymocyte globulin

CMV – Cytomegalovirus

CTLs – Cytotoxic Lymphocytes

EBV – Epstein Barr Virus

ELISPOT – Enzyme-Linked Immunospot

GvHD – Graft Versus Host Disease

IFN- γ - Interferon gamma

LCL – Lymphoblastoid cell line

PBSC – Peripheral blood stem cell

PCR – Polymerase chain reaction

SAEs – Serious adverse events

VSTs – Virus-specific T cells

INTRODUCTION

Adenovirus (ADV) can cause significant morbidity and mortality in children following allogeneic haematopoietic stem cell transplantation (HSCT) when cellular immunity is compromised [1,2]. Surveillance using PCR based methods is now routine for ADV in many transplant centres and the incidence of virus detection has been reported to be between 17-27% in paediatric transplant recipients [3,4]. A major risk factor for ADV reactivation after HSCT is the use of T cell depleted grafts. This includes the use of in vivo serotherapy such as Alemtuzumab (monoclonal anti-CD52 antibody) or thymoglobulin (polyclonal rabbit anti-thymocyte globulin [ATG]) to remove donor T cells that may cause acute Graft versus Host Disease (GvHD) [3,5-6]. The use of these agents prolongs reconstitution of donor-derived immunity post-transplant, and along with immunosuppressive agents, can render transplant recipients particularly vulnerable to viral reactivation with CMV, EBV, or ADV [3,5,6-8]. Whilst antivirals such as Cidofovir, Brincidofovir and Ribavirin are used for the treatment of ADV, they are associated with toxicity [9-10]. It has been demonstrated that reconstitution of virus-specific cellular immunity is essential to control viral infection after allogeneic HSCT [7-8]. Over the past two decades, adoptive transfer of donor-derived virus-specific T cells has been investigated to prevent and treat ADV and other viral infections post-HSCT. Feasibility studies have employed the use of engineered lymphoblastoid cell lines (LCL) or dendritic cells and required expansion periods of up to 6 – 8 weeks [11-13]. A more rapid strategy was described by Feuchtinger et al., [14] using the interferon- γ (IFN- γ) capture system (Miltenyi Biotec, Bergisch Gladbach, Germany) and a shorter expansion period (median 18 days). A similar approach of enrichment of IFN γ secreting cells but without *ex vivo*

expansion (ADV-specific T cells were infused directly after 24 hours) was evaluated in the study by Feucht and colleagues [15] and in five patients in London, with ADV-specific T cells derived either from the original donor (n=3) or third-party haploidentical parents (n=2) [16]. Three patients cleared ADV in blood after a single infusion of 10^4 T cells/kg and had demonstrable ADV-specific T cell in circulation detected by IFN- γ secretion assay. However, recalling of unrelated donors created delays and these children received cell therapy after an average of 80 days after original stem cell graft whilst the median day to viral reactivation was 15 days [6]. Here we describe the results of a phase I/II first-in-man trial of using donor-derived ADV CTLs (ASPIRE trial EudraCT number 2011-001788-36) aiming to provide timely, donor derived cell therapy to high-risk paediatric HSCT recipients. The trial aimed to pre-manufacture ADV-specific T cells using a 10-day peptide-pulse strategy with cells collected either from a sample of GCSF mobilized peripheral blood transplant harvest or a separate steady state whole blood venesection. This aimed to ensure that a cell therapy product was available within a month of transplant, by the time viral reactivation was first expected and after the effects in vivo serotherapy had resolved.

METHODS

Study design

The study was an open label phase I/II study to investigate the safety of pre-emptive administration of Adenovirus-specific T cells (Cytovir[®] ADV) given to high-risk paediatric patients post allogeneic HSCT to treat reactivation of adenoviraemia. Primary endpoints were safety related based on serious adverse events (SAEs) including GvHD and secondary endpoints evaluated antiviral response based on viral

loads and use of antiviral drugs. This was primarily a safety study with limited descriptive statistical analysis.

Participant details

Paediatric patients undergoing allogeneic HSCT using T cell depletion from a matched unrelated, mis-matched unrelated or family donor, or haploidentical donor were eligible for recruitment to the study. Patients were recruited from three UK centres: Great Ormond Street Hospital (London), The Great North Children's Hospital (Newcastle-upon-Tyne), and Royal Manchester Children's Hospital (Manchester). The study design is outlined in Figure 1. The study protocol was approved by the West London National Research Ethics Committee. Patients and donors gave written informed consent prior to enrolment. Patients were eligible for administration of ADV-specific T cells if at any time post HSCT they developed two consecutive positive ADV PCR results of >1000 copies/mL in blood; but the product was not administered until 28 days post allo-HSCT due to prolonged effect of prior conditioning serotherapy on T cell viability. Patients were excluded if they had significant GvHD (\geq grade II) or established pneumonitis or hepato-biliary disease. Donors for suitable trial participants were selected for the manufacture of Cytovir[®] ADV from those already scheduled to undergo an allo-HSCT at the three study sites. Donor registries that had approved the study protocol and consent procedure included Anthony Nolan Trust (UK), Welsh Bone Marrow Donor Registry, ZKRD (the German National Registry of Blood Stem Cell Donors), DKMS (Germany) and National Marrow Donor Program (USA). Donors were given the opportunity to consent to the use of either a portion of their original stem cell donation or a whole blood sample for the manufacture of Cytovir[®] ADV for their recipient. Following confirmation of written informed consent, a 5 mL aliquot of mobilised apheresis

product or a 100 mL blood sample by venepuncture was taken into a transfer bag for expansion of ADV-specific T cells. The minimum number of cells required in the starting material was approximately 4×10^7 CD3⁺ T cells. Donors were enrolled between January 2013 and May 2016 and infusions administered between April 2013 and July 2015.

Transplants

Allo-HSCT were undertaken with matched unrelated, mismatched unrelated, family donors, or haploidentical donors; with in vivo (ATG or Alemtuzumab) or ex vivo (CD3 alpha-beta/CD19) T cell depletion. Of the 8 enrolled patients, one (A1-02) received mismatched family donor bone marrow. Seven patients received peripheral blood stem cells: three from a mismatched unrelated donor (Patients A1-03, A1-13 and A3-01), two from a matched unrelated donor (Patients A1-04 and A1-42) and two from a haploidentical donor (Patients A1-17 and A2-06) (Table 1).

Antiviral drug therapy was administered as standard of care according to institutional guidelines regardless of Cytovir[®] ADV infusion. Patients received Cidofovir 5mg/kg weekly for 2 weeks if blood PCR > 1,000 copies/mL on 2 consecutive tests. Maintenance therapy was continued at 5mg/kg two weekly if adenovirus PCR > 10,000 copies/mL or evidence of organ disease.

Manufacture of ADV-specific T cells

ADV-specific T cells were generated as recently described [18]. Briefly, peripheral blood mononuclear cells (2×10^7) derived from either whole blood (100mL blood collection from bone marrow donors) or mobilised apheresis (5mL) from peripheral blood stem cell donors were isolated by density gradient separation (Ficoll-Paque, GE

Healthcare). ADV-specific T cells were selectively expanded with 5ng/peptide/mL GMP-grade overlapping peptides from AdV5 (AdV5 Hexon PepTivator; Miltenyi Biotec) and cytokines IL4 (200 ng/mL, CellGenix) + IL7 (10 ng/mL, CellGenix) in a cell expansion system (G-Rex 10, Wilson Wolf) and incubated at 37°C/5% CO₂ for total of 10 days. Cells were then harvested, washed, counted and re-suspended at the appropriate concentration in cryopreservation medium containing Human Serum Albumin (HSA) and Dimethyl Sulfoxide (DMSO) prior to controlled rate freezing for storage in liquid nitrogen vapour. Cells were cryopreserved in 2 dose aliquots: 1 x 10⁴ and 1 x 10⁵ CD3⁺ T cells/kg of recipient weight in labelled CryoStore™ bags (OriGen Biomedical).

ADV-specific T cell infusion

Cytovir® ADV was released for administration if it fulfilled the following criteria: purity > 80% CD3⁺ T cells, viability > 70% CD3⁺ T cells, passed microbiological sterility tests, potency $\geq 10^2$ IFN γ^+ T cells per kg. The product was administered as a single intravenous infusion following allogeneic HSCT D+28 or later on PCR evidence of ADV viraemia (two consecutive ADV level >1000 copies/mL). Previous data from Cytovir® ADV manufactured from healthy adult donors demonstrated low, but detectable, levels of alloreactivity in the T-cell product [18]. In order to minimise risk of GvHD, an initial cell dose of 1x10⁴ CD3+/kg was chosen, with 1x10⁵ CD3+/kg as subsequent dose if required. **This dose was chosen based on our previous experience in haploidentical procedures [16] and evidence from a meta-analysis of 100 patients undergoing DLI which suggested that a maximum dose of 1 x 10⁵ CD3+/kg is safe for a DLI from a matched unrelated donor [19]. An initial cell dose of 1x 10⁴ CD3+/kg was chosen as a safe starting dose with**

provision for 10-fold escalation if required. Characterisation of manufactured products along with ADV specificity has been recently published [18].

Patient Monitoring

Routine screening for adenoviraemia was performed on whole blood by quantitative polymerase chain reaction (PCR) for ADV DNA twice per week. Once enrolled on the study, patients were monitored at these approximate time points post Cytovir[®] ADV administration: 14, 30, 60, 90, 120, 150 and 180 days. If patients received a second dose they were monitored for a further 180 days. Immune reconstitution was traced by lymphocyte subsets (CD3⁺CD4⁺, CD3⁺CD8⁺ and CD3⁻/CD16⁺CD56⁺) and chimerism studies performed by short tandem repeat variability as described previously [17]. IFN γ enzyme-linked immunospot assay (ELISpot) was performed at 30, 90 and 180 days post infusion when counts were sufficient [18].

RESULTS

Donor and recipient enrolment and treatment

Between January 2013 and May 2016, 97 donors were screened, and 92 donors donated starting material (72 PBSC and 20 whole blood donations). 83 Cytovir[®] ADV products were released for infusion. There were 6 manufacturing failures in total; 3 products did not meet release criteria and 3 products failed due to technical problems. Another 3 successfully manufactured products could not be released for the study as the patients did not meet inclusion criteria.

Adverse events

Serious adverse events were encountered in 3/8 treated patients. One child developed pancreatitis 9 days after cell infusion coinciding with a rise in ADV load in blood up to 4×10^5 copies/mL, although concomitant medications may have been contributory. The patient made complete recovery after 39 days with ADV load undetectable. One patient initially cleared ADV but developed stage II skin GvHD 64 days after infusion (D +161 post HSCT), which progressed to stage IV, steroid refractory gut GvHD. Systemic immunosuppression was subsequently associated with late reactivation of Adenovirus which culminated in respiratory failure and death 23 months after transplant. One patient developed serious neurological complications that were subsequently attributed to a novel viral pathogen. This 18 month-old subject received ADV CTL on D+28 after an uncomplicated 10/10 HLA-matched unrelated donor transplant for Cartilage Hair Hypoplasia associated immunodeficiency and cleared viraemia. He developed a progressive encephalopathy two weeks later, and this was subsequently attributed to cerebral Astrovirus infection and the patient died 9 months after HSCT as previously reported [20].

Efficacy

8 patients received an initial dose of 1×10^4 /kg total CD3+ lymphocytes between D+28 and D+97 post HSCT. One patient also received a second dose of 1×10^5 /kg total CD3+ lymphocytes on D+71 as ADV viral load continued to rise in blood after the first dose. All patients experienced reduction in ADV viral load in blood after infusion with mean time to absence of ADV viraemia of 56 days (range 15-127 days). ADV viraemia was undetectable from Day 30 onward in Patient A2-06, from Day 60 in Patients A1-03, A1-13 and A1-42, from Day 120 in Patients A1-04 and A1-17, from Day 150 in Patient A3-01, and from Day 30 post second dose (i.e.,

approximately 60 days post first dose) in Patient A1-02. Six of 8 patients received concomitant ADV-antiviral medication for a mean duration of 51 days. Adenovirus-specific T cells were detectable by ELISpot in the peripheral blood of all six patients with available data and persisted until the final time point assessed (at least Day 90).

ADV-specific T cell reconstitution after adoptive T-cell transfer (Table 2, Figure 3)

All patients with available ELISpot data (6 of 8 patients; no data available for Patients A1-03 and A1-04 due to persistent lymphopaenia) exhibited ADV-specific T cells in peripheral blood starting at Day 14 or Day 30 (post second dose in case of Patient A1-02), and these remained detectable until at least day 90 after infusion.

DISCUSSION

We have previously reported the health care and financial burden of viral reactivation after HSCT. Bespoke donor derived cellular therapy for virus reactivation can provide life-saving therapy, but the manufacture and supply of such products is challenging. Delays in recalling donors for additional cell collection is particularly problematic and time consuming.

We report phase I/II data for Adenovirus-specific T cells manufactured from adult donors, the majority from volunteer registries, and used pre-emptively in high-risk paediatric patients. The study required donations to be collected from 5 registries in 3 countries. In total 97 donors were screened, 92 donations were received, and 83 products were successfully manufactured by taking a small aliquot of cells from routine mobilised peripheral blood harvests or from whole blood.

Across three sites, 8 patients were treated from 83 products manufactured. All treated patients had experienced a reduction in ADV viral load in blood from levels of greater than 20 million copies/mL. There were no acute infusion-related adverse events, and in 6 treated patients in-vitro ADV-specific responses using a ELISpot of IFN γ cytokine release were demonstrated. Serious adverse events were recorded in 3 patients, two of whom died. In one, encephalitis was attributed to Astrovirus after detailed analysis by deep sequencing of brain tissue but in another patient severe GvHD arising in the context of Adenovirus related inflammation became refractory and life-limiting. GVHD is the major concern in such clinical trials of adoptive ADV T cell transfer and one patient in another trial of peptide pulsed cells developed severe GvHD after a similar T cell dose (1×10^4 CD3 $^+$ /kg) [21]. Others reported no serious GvHD in a group of 30 patients treated with a lower mean T-cell dose of 4.1×10^3 CD3 $^+$ cells/kg generated by ADV hexon stimulation and enrichment of IFN- γ secreting cells [15].

The study provides a demonstration of feasibility for pre-emptively manufacturing ADV-specific cell therapy for high-risk paediatric patients after transplant, as well as good first evidence of clinical activity. A larger randomised Phase III study will be required to assess clinical efficacy further. The ability to generate virus-specific cells from harvested peripheral blood stem cell collections after GCSF mobilisation was encouraging, but the logistics of coordinating production from fresh collections is a major challenge to wider application and studies are underway to evaluate the possibility of using cryopreserved starting materials. In this Phase 1 study a large number of products were manufactured but not infused because patients did not meet stringent criteria set to limit use only in those developing viraemia. Beyond safety testing, larger phase efficacy studies will help determine optimal timing and dosing

regimens for a more economical approach. **In addition, for patients receiving grafts from virus-seronegative donors, one alternative option for virus-specific T cells is to use partially HLA-mismatched third-party T-cells. In a recent multicentre study, banked third-party virus-specific T cells (VSTs) were administered to 50 patients with severe, refractory CMV, ADV or EBV infections [22]. The cumulative rates of complete or partial responses at 6 weeks post infusion were 74% for the entire group with only 2 patients developing de novo GvHD (grade 1).** Overall, a combination of directed antiviral drug therapy and cell based approaches should offer effective solutions to problematic virus related complication after transplantation.

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Disclosure of interest

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