



Disseminated adenovirus infection after allogeneic stem cell transplant and the potential role of brincidofovir – Case series and 10 year experience of management in an adult transplant cohort

Isobel D. Ramsay^a, Charlotte Attwood^b, Dianne Irish^a, Paul D. Griffiths^{a,c}, Charalampia Kyriakou^{b,1}, David M. Lowe^{c,d,*,1}

^a Department of Virology, Royal Free Hospital London, UK

^b Department of Haematology Royal Free Hospital London, UK

^c Institute of Immunity and Transplantation, Royal Free Campus, University College London, UK

^d Department of Immunology, Royal Free Hospital London, UK

ARTICLE INFO

Keywords:

Adenovirus
Brincidofovir
Bone marrow transplant

ABSTRACT

Background: Adenovirus infection is a recognized complication following haematopoietic stem cell transplantation. We present a review of our experience of these infections in our transplant cohort over 10 years including 3 patients treated with the novel antiviral brincidofovir.

Objectives: We aimed to describe the presentation, response to treatment and outcomes of adult stem cell transplant patients with disseminated adenovirus infection.

Study design: All adult cases of disseminated adenovirus infection following haematopoietic stem cell transplant in our unit between 2005 and 2015 were identified. Transplant details and data on timing of diagnosis, course of infection, viral co-infection and treatment were collected.

Results: Of 733 patients transplanted, 10 patients had disseminated infection, including 4 male and 6 female patients with median age of 36.5 (range 19–59) years. 6/10 received an allograft from an unrelated donor. Median post-transplant time to detection of viraemia was 67 days (range 20–1140 days). Median peak viral load was 3133 copies/ml (352–11,000,000) in survivors received cidofovir alone, one cidofovir then brincidofovir and two brincidofovir alone. 8/10 p and 1,580,000 copies/ml (41,999–3,000,000) in those who died.

Five patients had a decrease in viral load following antivirals and/or reduction in immunosuppression including all on brincidofovir. Three died on treatment.

Conclusions: Disseminated adenovirus infection is uncommon in adult transplant patients and uncertainties remain surrounding effective treatment. In our cohort, brincidofovir has shown promise in treatment of adenoviral infection. However, randomized controlled studies are required to confirm this impression.

1. Background

Adenovirus infection is a recognized cause of morbidity and mortality following haematopoietic stem cell transplantation (HSCT) occurring in 5% to 47% of recipients [1–7].

Infection is often asymptomatic but may result in end-organ disease including colitis, pneumonitis, hepatitis, nephritis, haemorrhagic cystitis, conjunctivitis, encephalitis or multi-site disease following viraemic spread [8]. More commonly seen in the paediatric population [9], disseminated disease may occur in adult transplant recipients and carries a high mortality of up to 26% [10]. Reported risk factors include

T cell depleting conditioning regimes [11], acute graft versus host disease (GVHD) [9], unrelated donor allograft [3] and use of alemtuzumab or antithymocyte globulin (ATG) [12].

Diagnosis of disease is typically made by combining clinical features with detection of viral DNA using polymerase chain reaction (PCR) or identification of viral inclusions on histopathology. Virus detection does not in itself prove significant end-organ disease, but detection at more than one site and increasing viral load, especially in blood, is taken to indicate a high risk. Management in these circumstances is orientated towards reducing viraemia. Interventions include reducing immunosuppression and consideration of antivirals; because no

* Corresponding author at: Institute of Immunity and Transplantation, University College London, Royal Free Campus, Pond Street, London, NW3 2QG, UK.

E-mail address: d.lowe@ucl.ac.uk (D.M. Lowe).

¹ These authors contributed equally.

antiviral drugs are currently licensed for the treatment of adenoviral disease, such treatments are necessarily investigational. Adoptive T cell immunotherapy holds promise as a treatment [13] although its widespread use is limited by the time-intensive nature of generating virus specific T cells [14]. Intravenous immunoglobulin (IVIG) has also been used in limited cases [15,16].

The published information on antiviral medications for adenovirus disease, including cidofovir and ribavirin, is limited at present to case series and small non-randomized studies [17]. Cidofovir is an acyclic phosphonate nucleotide analogue whose diphosphate is an inhibitor of the viral DNA polymerase and reduces adenovirus replication in vitro [18]. Its use is limited by side effects including significant nephrotoxicity [19] which can be reduced by pre-hydration and probenecid to decrease tubular secretion of the drug. This introduces a significant management problem in patients undergoing HSCT who often receive nephrotoxic medication for GVHD prophylaxis and antimicrobial, antifungal and antiviral agents.

Brincidofovir (CMX 001, Chimerix Inc, Durham, North Carolina, USA) is an unlicensed orally bioavailable lipid conjugate of cidofovir which demonstrates greater intracellular uptake than cidofovir with a lower propensity for renal accumulation [20,21]. Brincidofovir has activity against adenovirus in immunosuppressed animal models [22] and is currently under investigation for adenovirus infection in Phase III trials (ClinicalTrials.gov Identifier: NCT02087306).

Here we report 3 cases of disseminated adenovirus infection treated with brincidofovir and relate these to our experience of treating disseminated adenovirus infections in our transplant cohort over 10 years.

1.1. Retrospective review of transplant cohort

All adult cases of adenovirus infection following haematopoietic stem cell transplant managed by our unit between January 2005 and February 2015 were retrospectively identified by searching the virology department database. The screening strategy for adenoviral infection changed over the 10 year period. In the year 2005–06, our laboratory carried out a pilot of routine screening: blood adenovirus PCR was sent in alternate weeks post transplant. However, there were no cases of disseminated infection detected in this time and on this basis, it was decided to move away from routine screening. From that point on, blood samples for adenoviral PCR have been sent in patients with clinical suspicion for infection only. CMV and EBV are routinely screened for by PCR in blood weekly (EBV) or twice weekly (CMV) for the first 90 days post transplant, allowing pre-emptive therapy of CMV viraemia. We extracted basic patient, disease and transplant data (age, sex, transplant type, conditioning, site of sample(s)) on all patients with a positive PCR for adenovirus in any clinical sample, and more extensive data (post-transplant immunosuppression, time of diagnosis in relation to transplant, course of infection, adenovirus treatment and clinical outcome) on patients with disseminated infection, defined as detection of adenovirus from 2 or more sites in the presence of viraemia with compatible symptoms [23]. Relevant clinical data were collected from case notes.

2. Results

2.1. Patient characteristics

Over the past 10 years, our unit has carried out 733 HSCTs of which 152 underwent allogeneic myeloablative (MAC), 277 reduced intensity conditioning (RIC) and 312 received autologous haemopoietic stem cell transplantation (ASCT). Of these 44 had adenovirus DNA detected at one or more sites by PCR. These included 20 females and 24 males with a median age at transplantation of 40 (Range 17–66). Three received autologous stem cell transplantation. Of those receiving allografts, 9 patients were treated with MAC (sibling donor $n = 5$) and 32 with RIC Allo SCT (sibling donor $n = 18$).

2.2. Site of infection

The sites most commonly infected were gastrointestinal (GI) tract ($n = 25$), respiratory tract ($n = 21$) and urinary tract ($n = 6$). In addition 1 patient had adenovirus detected in CSF and 3 on eye swabs.

Forty-three of the 44 patients who had adenoviral DNA detected at one organ site also had their blood tested by adenovirus PCR to look for disseminated infection. Seventeen patients had viraemia with a median peak viral load of 3344 (352–11,000,000). Ten patients (23%) including cases 1–3 (detailed below) met criteria for disseminated infection.

2.3. Characteristics of patients with disseminated infection

The characteristics of the 10 patients with disseminated infection are summarized in Table 1. They included 4 male and 6 female patients with a median age of 36.5 (range 19–59) years, with 8/10 receiving T cell depleted grafts. Median post-transplant time to detection of viraemia was 65 days (range 20–1,140 days). The median peak viral load was 3133 copies/ml (352–11,000,000) in those who survived and 165,415 copies/ml (41,999–3,000,000) in those who did not. Median duration of viraemia was 14 days (range 7–67) in survivors and 21 days (range 2–103) in those who died. As shown in Table 1, co-infection with other viruses during the hospital admission was common.

2.4. Treatment and outcomes

Five patients received IV cidofovir alone, one cidofovir then brincidofovir (Case 1 described below) and two brincidofovir alone (Cases 2 and 3). Cidofovir doses ranged from 1.5–2 mg/kg 3 times a week and brincidofovir doses from 50 to 100 mg twice weekly. Total duration of antiviral treatment ranged from 2 to 63 days. Among patients given cidofovir, treatment was discontinued in two cases due to nephrotoxicity, in one case was changed to brincidofovir due to lack of efficacy (Case 1), and two patients died with ongoing viraemia.

Information on immunosuppression was available for 9 patients and 6 of these had their immunosuppression reduced. Two patients with disseminated infection only had their immunosuppression reduced and did not receive antivirals. Only two patients received IVIG as part of their treatment. Seven patients became aviraemic (median reduction in viral load of 1.20 log (0.25–4.74log)) and one had a 1.19 log decrease in viral load (case 2). Three died while on treatment (a mortality rate of 30% in those with disseminated infection), although adenovirus disease was only thought to be the primary cause of death in 1 patient (case 4). All those who died had an absolute lymphocyte count of less than $0.25 \times 10^9/L$ at the point of diagnosis.

3. Case reports

3.1. Cases 1–3 from Table 1 who received brincidofovir as part of their treatment are described in detail below.

3.1.1. Case 1

A 59 year old woman underwent a fludarabine, melphalan, alemtuzumab matched unrelated donor peripheral haematopoietic stem cell transplant (MUD Allo SCT) for treatment of acute myeloid leukaemia in second remission. Cyclosporin A and mycophenolate mofetil were given for GVHD prophylaxis. On day ten following transplantation, the patient developed severe diarrhoea (6–8 L daily). Bacterial stool culture and *C.difficile* toxin tests were negative. Her neutrophil count was $0.81 \times 10^9/L$. Examination of stool and blood samples by PCR on day 20 post-transplant (in-house assay adapted from Heim et al. [24]) detected adenovirus. Quantitative PCR showed 8872 copies/ml of whole blood. Flexible sigmoidoscopy revealed patchy colitis with chronic damage and regeneration without features diagnostic of current acute GVHD on histology.

Download English Version:

<https://daneshyari.com/en/article/5667973>

Download Persian Version:

<https://daneshyari.com/article/5667973>

[Daneshyari.com](https://daneshyari.com)