EXCEPTIONAL CASE

The use of intravesical cidofovir for the treatment of adenovirus-associated haemorrhagic cystitis in a kidney transplant recipient

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ABSTRACT

Adenovirus is an important cause of haemorrhagic cystitis in kidney transplant recipients. The optimal treatment for adenovirus-associated haemorrhagic cystitis (AAHC) is unknown. Intravenous cidofovir may be effective, but nephrotoxicity is a major concern. The use of intravesical cidofovir for viral haemorrhagic cystitis has been reported in haematopoietic stem cell transplant recipients and may be associated with a lower risk of nephrotoxicity, but its use has not been reported in kidney transplant recipients. We report the use of intravesical cidofovir for the treatment of AAHC in a kidney transplant recipient, along with a review of the literature.

Keywords: adenovirus, cidofovir, intravesical, kidney, transplant

INTRODUCTION

Adenovirus infection is an important cause of haemorrhagic cystitis in kidney transplant recipients [1] and may result in allograft dysfunction, acute rejection, graft loss and even death. Intravenous cidofovir may be effective in the treatment of adenovirus-associated haemorrhagic cystitis (AAHC) in kidney transplant recipients, but nephrotoxicity remains a concern [1]. Intravesical cidofovir has been used on haematopoietic stem cell transplants patients [2–4] for viral haemorrhagic cystitis but not in kidney transplant recipients. We report the use of intravesical cidofovir for the treatment of AAHC in a kidney transplant recipient, along with a literature review.

CASE REPORT

A 59-year-old female was admitted for 3 days of fever, malaise and cough. She has end-stage renal disease due to autosomal dominant polycystic kidney disease and had received a preemptive kidney transplant from a living, ABO-compatible, single haplotype–matched donor 4 months ago. She had received three daily doses of intravenous methylprednisolone 500 mg for induction and was maintained on prednisolone, mycophenolic acid and tacrolimus. Her post-operative course was uncomplicated.

Initial workup was unremarkable except for leukopenia. Empirical aztreonam was initiated in view of penicillin allergy.
Although intravenous cidofovir may be effective [1], nephrotoxicity is a significant concern. Approximately 30% of non-kidney transplant paediatric patients receiving intravenous cidofovir for adenovirus infections developed nephrotoxicity and the risk appears to be dose dependent [5]. Up to 50% of patients develop nephrotoxicity when intravenous cidofovir is used in haematopoietic stem cell transplant patients [6]. In our review (Supplementary data), 3 of 13 kidney transplant recipients (23.1%) developed worsening of renal function after the administration of intravenous cidofovir for adenovirus infections and 5 cases (38.5%) had a >30% increase in serum creatinine from baseline after the completion of treatment. Nephrotoxicity is thought to be due to renal tubular necrosis caused by high intracellular concentrations of cidofovir. Hyperhydration and oral probenecid [1] have been proposed to reduce the risk of nephrotoxicity by reducing intracellular cidofovir concentrations, but its efficacy is unclear.

While the use of intravesical cidofovir has not been reported in kidney transplant recipients, it has been used in hematopoietic stem cell transplant patients [2–4]. In the cases reported (Table 1), visible haematuria resolved 2–8 days after initiation of intravesical cidofovir. Non-visible haematuria developed in 3 cases (23.1%) and visible haematuria in 2 cases (15.4%) of 13 kidney transplant recipients. In our review (Supplementary data), 3 of 13 kidney transplant recipients (23.1%) developed worsening of renal function after the administration of intravenous cidofovir for adenovirus infections and 5 cases (38.5%) had a >30% increase in serum creatinine from baseline after the completion of treatment. Nephrotoxicity is thought to be due to renal tubular necrosis caused by high intracellular concentrations of cidofovir. Hyperhydration and oral probenecid [1] have been proposed to reduce the risk of nephrotoxicity by reducing intracellular cidofovir concentrations, but its efficacy is unclear.

Computer tomography scan of the abdomen revealed cystitis and mild dilatation of the collecting system of the transplanted kidney without pyelonephritis or cyst haemorrhage in the native or transplanted kidneys. After extensive workup, only urine and blood polymerase chain reaction for adenovirus turned positive on Day 10.

A diagnosis of AAHC was made. The patient’s mycophenolic acid decreased on the same day (and eventually stopped on Day 13). In view of persistent visible haematuria and urinary symptoms, a single dose of intravesical cidofovir at 2 mg/kg diluted in 100 mL of 0.9% saline was instilled via a urinary catheter and was dwelled for 1 h on Day 11. The patient’s symptoms improved and visible haematuria was resolved by Day 16 of admission. On follow-up, 41 days after initial presentation, the patient was asymptomatic and her renal function had returned to baseline.

**DISCUSSION**

The optimal treatment of AAHC in kidney transplant recipients is unclear. Treatments reported include reduction of immunosuppression, antiviral therapy (such as cidofovir, ribavirin) and immunotherapy (such as immunoglobulins, T cell–based therapies) [1]. Among the antiviral agents, cidofovir has the most available supporting evidence [1] and has been found to have in vitro activity against all strains of adenovirus.

### Table 1. Use of intravesical cidofovir for AAHC (haematopoietic stem cell transplants)

| References | Patient characteristics | Onset after transplant (days) | Cidofovir dose | Outcomes |
|------------|-------------------------|-------------------------------|----------------|----------|
| Fanouregakis et al. [2] | 34-year-old male, CML, familial haploidentical BMT Fludarabine, melphalan, ATG, TBRT, cyclosporine, MMF, methylprednisolone GVHD on D27 | 105 | Intravesical 5 mg/kg diluted in 100 mL 0.9% NaCl, clamped 1 h BD × 2 on Day 132 and Day 137 | Viruria cleared D133 HC resolved  D139 |
| Sakurada et al. [3] | 63-year-old male MUD BMT, AML Fludarabine, blysulfan, TBRT, tacrolimus, methotrexate, MMF, prednisolone | 185 | Intravenous 1 mg/kg 3 times/week × 7 doses from D209 (but HC persisted) Intravesical 2 mg/kg in 100 mL NS infused over 15 min clamped 1 h on D265, D283 | Hydronephrosis, HC resolved ‘within a few days’, microhaematuria in 2 weeks D292 viruria resolved |
| Sakurada et al. [3] | 63-year-old male WM, MUD BMT Fludarabine melphalan (both ADV and BKV) Tacrolimus, methotrexate, prednisolone, gencitabine | 177 | Intravesical 5 mg/kg × 2 doses on D187, D188 | HC resolved “3 days later” |
| Aitken et al. [4] | 23-year-old female | 18 | Intravesical 2.5 mg/kg dwell 70 min × 1 dose | Pharmacokinetic and safety study Clinical outcomes not reported in detail. No adverse effects. Bioavailability 74%, half-life 2.7 h |

CML, chronic myeloid leukaemia; BMT, bone marrow transplant; ATG, anti-thymocyte globulin; TBRT, total body radiotherapy; MMF, mycophenolate mofetil; GVHD, graft versus host disease; 0.9% NaCl, sodium chloride 0.9% solution; HC, haemorrhagic cystitis; MUD, matched unrelated donor; AML, acute myeloid leukaemia; WM, Waldenstrom macroglobulinaemia; ADV, adenovirus; BKV, BK virus.
The optimal dosing of intravesical cidofovir is unknown. Dosing regimens ranged from 1 to 5 mg/kg, diluted in 100 mL of normal saline, infused via an indwelling catheter and dwelled for 1 h. In pharmacokinetic study [4], intravesical cidofovir resulted in significant variability in systemic absorption (1–74% bioavailability). Of six cases, one developed severe bladder spasms and could not tolerate a rechallenge. One patient developed nephrotoxicity [4], although it is not clearly attributable to cidofovir, as systemic absorption was only 4%.

CONCLUSION
Intravesical cidofovir may be a useful adjunct in the treatment of AAHC among kidney transplant recipients. Further studies need to be performed to investigate its efficacy, safety and optimal dosing.

SUPPLEMENTARY DATA
Supplementary data are available at ckj online.

CONFLICT OF INTEREST STATEMENT
None declared.

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