Pharmacokinetics and safety of intravesicular cidofovir in allogeneic HSCT recipients

Samuel L. Aitken1,2, Jian Zhou2, Shashank S. Ghantoji3, Dimitrios P. Kontoyiannis3, Roy B. Jones4, Vincent H. Tam2* and Roy F. Chemaly3

1Division of Pharmacy, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Unit 0090, Houston, TX 77030, USA; 2Department of Pharmacy Practice and Translational Research, University of Houston College of Pharmacy, 1441 Moursund St., Houston, TX 77030, USA; 3Department of Infectious Diseases, Infection Control, and Employee Health, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Unit 1460, Houston, TX 77030, USA; 4Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Unit 0423, Houston, TX 77030, USA

*Corresponding author. Tel: +1-832-842-8316; Fax: +1-832-842-8383; E-mail: vtam@uh.edu

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Objectives: The objective of this study was to evaluate the pharmacokinetics and safety of cidofovir administered via the intravesicular route to patients with haemorrhagic cystitis following allogeneic HSCT (allo-HSCT).

Methods: Patients with gross haematuria and confirmed BK or adenovirus viruria following allo-HSCT were prospectively enrolled in an open-label pharmacokinetic study (ClinicalTrials.gov registration: NCT01816646). Three hours after an oral probenecid dose (2 g), cidofovir (2.5–5 mg/kg in 50–100 mL of normal saline) was given via a transurethral catheter for up to 2 h of dwell time. Serial plasma samples were obtained over 24 h and assayed for cidofovir concentrations using LC-MS/MS. A custom pharmacokinetic model with a time-limited absorption compartment was fitted to the concentration–time profile of each patient. Systemic drug exposure was expressed as AUC0–24, by integrating the best-fit profile with respect to time.

Results: Six subjects (mean ± SD age = 38 ± 21 years) with baseline serum creatinine, 1.4 mg/dL were enrolled. Mean values for volume of distribution, clearance and elimination half-life were 19.5 L, 5.6 L/h and 2.8 h, respectively. Compared with the reported AUC0–24 for an equivalent intravenous dose, intravesicular instillation of cidofovir resulted in 1%–74% of the corresponding systemic exposure. Owing to primarily lower abdominal pain, only two patients were able to tolerate a 2 h dwell time. One patient developed a 50% increase in serum creatinine within 7 days of administration.

Conclusions: Intravesicular administration of cidofovir resulted in highly variable systemic exposures. The safety and efficacy of intravesicular cidofovir should be further evaluated before routine use.

Introduction

Haemorrhagic cystitis is a common toxicity following allogeneic HSCT (allo-HSCT).1 Early cases are frequently a complication of cyclophosphamide during the conditioning regimen, while late cases are usually due to viral infection (e.g. BK virus, adenovirus).2,3 There are no standard treatments for viral haemorrhagic cystitis, although the broad-spectrum antiviral cidofovir is active in vitro against both BK virus and adenovirus.6 Owing to the localized nature of haemorrhagic cystitis and the risk of nephrotoxicity associated with systemic use of cidofovir, the intravesicular route has sometimes been used for this infection following allo-HSCT.5,6 However, to our knowledge, no studies have evaluated the potential for systemic absorption of cidofovir and subsequent toxicity when used intravesicularly. We evaluated the pharmacokinetics and safety of intravesicular cidofovir in patients with BK virus or adenovirus haemorrhagic cystitis following allo-HSCT.

Methods

Study design

This was a single-centre, open-label, pharmacokinetic study in hospitalized allo-HSCT recipients with proven viral haemorrhagic cystitis (ClinicalTrials.gov registration: NCT01816646). Eligible adult (age ≥18 years) patients had haemorrhagic cystitis with gross haematuria or passage of clots and either BK or adenovirus viruria by PCR testing. Patients were excluded if they had renal dysfunction (serum creatinine >2.0 mg/dL and/or urine protein >100 mg/dL). This study was approved by the MD Anderson Cancer Center institutional review board. All patients provided written informed consent prior to participation.
Cidofovir administration

Patients were initially given a single dose of cidofovir (5 mg/kg actual body weight) in 100 mL of normal saline through a transurethral catheter with a 2 h dwell time. An oral dose of probenecid (2 g) was administered 3 h before bladder instillation. Oral or intravenous hydration was given before and after bladder instillation per routine care. Owing to poor tolerability after clamping of the catheter, the study protocol was amended after the first three patients and the cidofovir dose was reduced to 2.5 mg/kg in 50 mL of normal saline. All patients received continuous normal saline bladder irrigation, analgesia and other supportive measures per standard of care.

Pharmacokinetic analysis

Blood samples were obtained from each patient prior to and at 1, 2, 4, 14 and 24 h following the start of the instillation. The plasma cidofovir concentrations were determined using a validated LC-MS/MS method (Gilead, Foster City, CA, USA). A custom pharmacokinetic model with a time-limited absorption compartment was fitted to the concentration–time profile of each patient using ADAPT 5.7. Model fits were evaluated by the coefficient of determination. Systemic drug exposure (expressed as AUC0–24) was derived by integrating drug concentration with respect to time over 24 h. The bioavailability was calculated by dividing the best-fit AUC0–24 by that expected of an equivalent intravenous dose.8

Safety assessment

Safety assessments, including a complete blood count, electrolytes, blood urea nitrogen, serum creatinine, ALT, total bilirubin and urinalysis, were conducted at baseline and repeated twice weekly for 1 week and again at the end of 2 weeks. Urine and blood samples were collected at various timepoints for viral load determination. Nephrotoxicity, defined as a >50% increase in serum creatinine from baseline, was assessed through day 7 following cidofovir administration. All patients were followed for 30 days for determination of any serious adverse events.

Results

Cohort characteristics and pharmacokinetic analysis

Six subjects with normal renal function (baseline serum creatinine <1.4 mg/dL) were enrolled for this study. Pertinent demographic characteristics for each patient are presented in Table 1. Dwell time ranged from 0.5 to 2 h. Plasma concentration–time profiles of cidofovir were captured satisfactorily by the pharmacokinetic model (r² > 0.93). The mean values for volume of distribution, clearance and elimination half-life were 19.5 L, 5.6 L/h and 2.8 h, respectively. Intravesicular administration of cidofovir resulted in bioavailability ranging from 1% to 74% (Table 1).

Safety

One of six patients had a >50% rise in serum creatinine within 7 days of administration; the cidofovir bioavailability for this patient was estimated to be 4%. Four of six patients experienced one or more serious adverse effects (Table 1), although only one was attributed to the study drug (patient 1). Only two patients were able to tolerate the full 2 h dwell time. One patient developed severe bladder spasms following administration and did not tolerate a rechallenge. The patient subsequently received a systemic dose of cidofovir. Five of six patients had clinically improved cystitis at last follow-up, with one experiencing complete resolution and

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other with no change from baseline. The plasma and urinary viral loads did not vary significantly at any timepoint in relation to baseline values (Table 2).

**Discussion**

In this study of allo-HSCT recipients with proven BK virus or adenovirus haemorrhagic cystitis, intravesicular administration of cidofovir resulted in variable systemic absorption. One of six patients in our study developed nephrotoxicity; therefore, the potential for systemic toxicity following local administration should not be overlooked. While the serum creatinine returned to baseline value in this case, irreversible nephrotoxicity following topical administration of cidofovir has been described. The highest observed bioavailability occurred in the single patient with adenovirus-associated haemorrhagic cystitis, suggesting that differential viral pathogenesis and epithelial cytotoxicity may play a role in the extent of cidofovir absorption.

Other observed clinical characteristics, including acute/chronic graft-versus-host disease or cyclophosphamide administration, did not appear to correlate with the extent of cidofovir absorption, precluding the identification of patients who may be at the highest risk for toxicity.

Our findings provide, to some extent, insight on the potential effect of intravesicular cidofovir when added to best supportive care for viral haemorrhagic cystitis. Five of six patients had clinically improved cystitis at the last follow-up, in agreement with published case series and reports in adult HSCT recipients. Despite improved symptoms, none of the patients had significant reductions in plasma or urinary BK viral load, contrasting with findings that the resolution of haemorrhagic cystitis generally correlates with a reduction in plasma viral load. The correlation between viral load and clinical resolution of viral haemorrhagic cystitis requires further study in this patient population.

While potentially effective, the tolerability of intravesicular administration warrants consideration. Only two of six patients were able to tolerate the protocol-specified 2 h dwell time. Other case series have reported patient discomfort with administration, while general anaesthesia was required to facilitate administration in paediatric HSCT recipients. Other therapeutic modalities, including low-dose intravenous cidofovir or brincidofovir may be similarly efficacious and may have better tolerability than intravesicular cidofovir. Finally, the small sample size and non-comparative nature of this study prevents any firm conclusions regarding the efficacy as well as overall safety profile of intravesicular cidofovir from being made. However, the safety of the intravesicular route should be carefully monitored in future studies, as the systemic absorption may be significant.

In conclusion, the intravesicular administration of cidofovir in allo-HSCT patients with BK or adenovirus haemorrhagic cystitis resulted in variable, sometimes substantial, systemic absorption. The tolerability, safety and efficacy of intravesicular cidofovir should be further evaluated in relation to other potential treatments.

**Acknowledgements**

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**Transparency declarations**

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**References**

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