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Retrospective audit of the use of Cidofovir for the treatment of Adenovirus in paediatric haematopoietic stem cell transplant (HSCT) recipients; a single centre experience of variable dosing schedules over a seven-year period at the Royal Marsden Hospital

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INTRODUCTION

- Adenovirus (ADV) remains a major cause of mortality and morbidity in paediatric haematopoietic stem cell transplant (HSCT) recipients.
- Risk factors for ADV infection/disease include younger age, haploidentical or Unrelated Donor graft, Cord transplants , T, GVHD III–IV, severe lymphopenia, and treatment with alemtuzumab /ATG (T cell depletion).
- Increased mortality if detected early (<60 days post HSCT)
- Standard treatment is the antiviral drug cidofovir (CDV) which is used for controlling adenoviremia and preventing disseminated viral disease. However, this can be associated with renal toxicity and practice varies between centres regarding optimal dosing schedule.
- While at a standard dose of 5mg/kg once weekly for 2 doses and then once in 14 days has been reported as primary therapy for treatment of ADV infection in pediatric and adult HSCT patients, concern exists regarding potential nephrotoxicity.
- The risk of renal toxicity was mostly mild (low-degree proteinuria or mild elevation of serum creatinine), but approximately half had remaining signs of renal impairment after discontinuation of CDV.
- These associated adverse effects have limited the use of CDV for treatment of ADV infections in pediatric patients.
- To minimize potential toxicity of CDV, modified dosing regimens such as the use of 1 mg/kg three times a week have also been utilized.

AIM

- To do a retrospective audit of the cidofovir dosing schedules in children with adenovirus infection, undergoing haematopoietic stem cell transplantation (HSCT).
- To evaluate patient outcomes, drug efficacy, need for rescue therapy and renal toxicity in children with adenovirus infections post HSCT.

METHODS

- A retrospective chart review was conducted for all hospitalized patients at Royal Marsden Hospital who were prescribed CDV for adenovirus infection over a 7 year period from January 2011 through December 2018.
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- Data was collected from patient case records on the EPR in order to assess dosing efficacy, response to treatment and potential incidence of drug toxicity.
- The inclusion criteria was :
  - age between 1-18 years
  - Underwent a HSCT
  - Treated for adenoviremia with cidofovir
- Excluded :
  - Age above 18 year
  - Treated with cidofovir for other viral infections eg. BK virus
- Data was collected from patient records and compiled on MS Excel sheet. It was analysed using standard statistical variables like mean , median and percentages.

RESULTS

Sites involved

- All 28 episodes had positive blood ADV Polymerase chain reaction (PCR)
- ADV also detected in the stool (n=18/28, 64%),
- Nasopharyngeal aspirate (n= 10/28, 35.7%)
- Urine (n= 4/28, 14%)
- Liver (n= 2/28 , 7%)
- 6 patients (21.4%) were also noted to have positive urinary BK virus although this was not the primary reason for CDV treatment.

Onset of adenoviremia

- Time to AdV detection ranged from D5 to (D 162) D 867 (1/28) post stem cell infusion and 75 % (21/28) had infection within the first 60 days.
- 21 (75%) within the first 60 days of transplant and 7 post D+60

Treatment

- 12 episodes (12/28, 42.8%) were treated using 1mg/kg (thrice weekly) dosing regimen .
- 16 episodes (16/28, 57.1%) were treated with the 5mg/kg dosing regimen (5mg /kg once a week for 2 weeks followed by once every alternate week).

Dosing and treatment Outcomes

- 41% (5/12) of those on 1mg/kg dosing required **rescue therapy** as compared to 25% (4/16) on the alternate regimen – rescue therapy was Brincidofovir and change from 1mg/kg to 5mg/kg dosing).
- The time period needed for **clearance** of ADV on the 5mg/kg dosing schedule ranged from 4 to 60 days with a mean **duration of 22.1 days**
- The clearance on 1mg/kg regimen being 6 to 56 days with a mean duration of **26.4 days.**

HSCT / Conditioning	Numbers
Myelo-ablative conditioning	22
Reduced intensity conditioning	2
Autologous	1

Toxicity

- 9 children had evidence of renal toxicity (9/28, 32.1%) **with 1 needing** discontinuation of CDV after a single dose clearly attributable to medications(5mg/kg) .
- 8 had clearly definable AKI which settled upon completion of treatment .
- 5mg/kg regimen (7/16 , n= 43 %)
- 1mg/kg regimen (2/12 , n= 16.6%)
- There were co-existing nephrotoxic medications including CSA , Foscarnet , Acyclovir , Amphotericin B which were administered at the same time hence the renal toxicity could be cumulative.

1 episode of neutropenia post CDV directly attributable to it was observed.

	1mg/kg thrice a week regimen	5mg/kg once a week x 2 weeks regimen
Patient numbers	12/28, 42.8%	16/28, 57.1%
Renal toxicity	2/12 , n= 16.6%	7/16 , n= 43 % , 1 requiring cessation rest reversible
Cumulative total Dose	5- 12mg/kg	5-25mg/kg
Mean dose	8.57mg/kg	14.1mg/kg
Rescue therapy	5/12 = 41%	4/16 = 25%
Clearance time	6 - 56 days	4 - 60 days
Mean duration	26.4 days	22.1 days

Total duration of study	2011- 2018 – 7years single centre analysis
Total patients analysed Episodes	25 28
Gender	Males -14 / Females -11
Ages at transplant	2-17 years
Survival Outcomes	17 survived / 8 RIP (sepsis / GVHD). Mortality significantly attributed to adenoviremia (disseminated disease) 4 / 28 (14%)

CONCLUSIONS

- CDV was well tolerated in the majority of cases for the treatment of ADV infections..
- In terms of dosing schedule, 1 mg/kg 3 times per week appeared to be somewhat less nephrotoxic when compared to 5mg/kg regimen (reversible renal dysfunction).
- However, with this (1mg/kg) dosing schedule we noted a trend towards increased time to clearance and an increased need for alternate rescue therapy.
- There was also increased outpatient attendance as a result of the thrice weekly schedule.
- Novel therapies are needed for HSCT recipients to reduce the burden and mortality of ADV disease and its associated toxicities.
- Donor-derived ADV-specific CTLs are an option for clinically non-responding patients.
- Oral brincidofovir 2 mg/kg twice weekly is an excellent option as a rescue therapy for ADV infections.

STANDARDS

Positive Adenoviremia :

- All patients with whole blood PCR positive results
  - one single value >1000 copies/ml
  - two consecutive samples showing rising values >100 copies/ml.
- Two non-blood sites being adenovirus positive

Dosing regimens used :

5mg/kg once a week for first 2 weeks followed by once every 2 weeks
1mg/kg thrice weekly

Clearance was defined as 2 blood PCR samples being negative.

Renal toxicity identified as per KDIGO international staging

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