Brincidofovir Decreases Adenovirus Viral Burden, Which is Associated With Improved Mortality in Pediatric Allogeneic Hematopoietic Cell Transplant Recipients

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539

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BACKGROUND

Adenovirus (AdV) infection is an important cause of morbidity and mortality after hematopoietic stem cell transplant (HSCT)

- In single-center studies, higher peak AdV viral loads have been correlated with higher mortality rates in pediatric allogeneic (allo)-HSCT recipients.[1, 2]
  - One study noted 44% mortality in those with AdV viremia >10,000 copies/mL versus 12% mortality in those with viremia <1000 copies/mL.[2]
- Robust multicenter data are needed to fully evaluate the relationship between AdV viral burden and mortality.
- Off-label use of intravenous cidofovir has been used to control AdV viremia in HSCT recipients but it does not lead to resolution of AdV infection without immune reconstitution.[3]
  - Cidofovir is associated with significant dose-limiting nephrotoxicity.[4]

Currently, there are no approved treatments for AdV infection. Brincidofovir (BCV) is an orally-bioavailable lipid conjugate of the nucleotide analog cidofovir that is being developed for this indication

- BCV has demonstrated antiviral activity against all clinically relevant AdV subtypes.[5, 6]
  - It is delivered directly into the intracellular space via its lipid conjugate, where it is converted to the active compound, cidofovir diphosphate.[6]
  - Lipid conjugation provides improved oral bioavailability for BCV as compared with cidofovir, and results in a higher intracellular concentration of cidofovir diphosphate.[3]
  - BCV limits the concentration of cidofovir in plasma and, together with the inability of BCV to be transported by organic anion transporter (OAT1), results in a lower risk of nephrotoxicity.[7]
- BCV treatment has shown potential for the treatment of serious AdV infection in expanded access or emergency use protocols.[3, 8-12]
  - In a recent retrospective, multicenter study of 47 pediatric HSCT recipients with AdV viremia, the median time to undetectable AdV viremia with BCV was 4 weeks (range, 2-9 weeks). This was significantly less than the 9 weeks (range, 3-15 weeks; $p<0.005$) observed with cidofovir.[3]
  - Only 1 patient required interruption of BCV treatment for gastrointestinal adverse events (AEs; of severe abdominal cramps and diarrhea).[3]
- In a randomized, placebo-controlled, multicenter, Phase 2 study of BCV treatment for the prevention of AdV disease, diarrhea was the most common AE in all groups (57% BCV BIW; 38% BCV QW; 28% placebo), but it led to treatment discontinuation in only 1 patient (who received BCV QW).[13]
- In clinical studies, BCV therapy has not demonstrated any hematologic toxicity or myelotoxicity.[8, 13]
- The open-label, single-arm AdVise study of oral BCV treatment of serious AdV infection in immunocompromised pediatric and adult patients showed rapid clearance of AdV from plasma.[14]

Area Under the viremia-time Curve (AUC) is a virologic endpoint that quantifies the severity of disease in acute lytic viral infections such as AdV[15, 16]

- This virologic measure has been used as a primary endpoint in Phase 2 and 3 studies of other investigational antivirals.[17-19]

OBJECTIVE

- To evaluate various measures of viral response and to explore the association between plasma AdV viral burden (measured by time averaged AdV AUC [AAUC]) and survival among pediatric allo-HSCT recipients with a clinically relevant AdV infection and receiving oral BCV treatment in the AdVise study.

METHODS

Study Design

- AdVise (CMX001-304; NCT02087306) was an open-label, single arm, multicenter study that enrolled patients in the US between March 2014 and April 2016 (primary analysis have been presented previously).[14]
- Pediatric (age ≥2 months) and adult patients with AdV infection were followed for the 36 weeks post first BCV dose.
- AdV DNA (copies/mL) in plasma was measured by a designated central virology laboratory (Viracor-IBT Laboratories, MO, USA) using quantitative polymerase chain reaction.
- BCV suspension or tablets (100 mg for patients ≥50 kg and 2 mg/kg for those <50 kg) were administered orally BIW for 12 weeks, with treatment extensions permitted for ongoing or recurrent AdV infection.

Data Analysis

- This post hoc analysis evaluated the correlation between AdV viral burden over time and survival outcomes in the subgroup of pediatric allo-HSCT recipients (≤18 years of age) with clinically relevant AdV infection (defined as AdV ≥1000 copies/mL in plasma) within the first 100 days post-HSCT.
- Clinical and virologic endpoints were determined:
  - The proportion of patients achieving undetectable AdV viremia.
  - Reductions from Baseline in AdV viremia.
  - Time to first undetectable AdV viremia.
  - Number of days of undetectable AdV viremia.
  - Time to <1000 AdV copies/mL.
  - AdV AUC (Area Under the viremia-time Curve).
  - Time averaged AdV AUC (AAUC; i.e., AUC divided by the number of days of follow-up over the 12 weeks after first BCV dose).
  - Survival at Week 36.
- Undetectable AdV viremia results were imputed at 99 copies/mL (1 less than the lower limit of detection) and detectable results not quantifiable were imputed at 189 copies/mL (1 less than the lower limit of quantification).
- Comparisons of survival were conducted using Kaplan-Meier methods and log rank tests; linear correlations were analyzed using regression methods; and the comparison between 12-week AdV AAUC in those who survived versus those who died during the first 36 weeks post first BCV dose was conducted using a Satterthwaite *t*-test.

RESULTS

Patient Demographics and Clinical Characteristics

- Of the 100 pediatric allo-HSCT recipients enrolled in the AdVise trial, 40 presented with clinically relevant AdV viremia (≥1000 copies/mL) in the first 100 days post-transplant and were included in this analysis (**Tables 1** and **2**).
  - Among these, most patients were <6 years of age (70%).
  - The median AdV viremia at Baseline was 4.5 $\log_{10}$ copies/mL, and 83% of patients were symptomatic.
  - At enrollment, 60% of patients had been treated previously with cidofovir.

Table 1. Baseline patient demographics and clinical characteristics

		(n=40)
Age (years)	Median (IQR)	3 (1-7)
	<2	13 (33%)
	2-<6	15 (38%)
	6-<12	7 (18%)
	12-<18	5 (13%)
Race	White	28 (70%)
	Black	7 (18%)
	Asian	2 (5%)
	Other	3 (8%)
Sex	Female	16 (40%)
	Male	24 (60%)
Time post-HSCT of first BCV dose (days)	Median (IQR)	43 (16-61)
	<28	18 (45%)
	≥28	22 (55%)
Acute GvHD	Any	6 (15%)
	≥ Grade III	4 (10%)
AdV viremia ($\log_{10}$ copies/mL)	Median (IQR)	4.5 (3.7-6.0)
AdV infection	Symptomatic	33 (83%)
	Asymptomatic	7 (18%)
Prior cidofovir treatment within 30 days[†]	None	16 (40%)
	<10 mg/kg	18 (45%)
	≥10 mg/kg	6 (15%)
Other concurrent dsDNA virus viremia at Baseline[‡]	BKV	12 (30%)
	CMV	8 (20%)
	EBV	2 (5%)

Data are n patients (%), unless otherwise stated.
[†]Cumulative dose within 30 days of Baseline. [‡]Patients could have had ≥1 concurrent viremic dsDNA virus infection alongside AdV viremia.
AdV, adenovirus; BCV, brincidofovir; BKV, BK virus; CMV, cytomegalovirus; dsDNA, double-stranded deoxyribonucleic acid; EBV, Epstein-Barr virus; GvHD, Graft vs Host Disease; HSCT, hematopoietic stem cell transplant; IQR, interquartile range.

Table 2. Allo-HSCT characteristics at Baseline

		(n=40)
Conditioning regimen	Myeloablative	24 (60%)
	Non-myeloablative	16 (40%)
Graft source	Cord	8 (20%)
	Bone marrow	19 (48%)
	Peripheral blood stem cells	13 (33%)
Donor type	Haploidentical	7 (18%)
	Mismatched	4 (10%)
	Matched unrelated	25 (63%)
	Matched related	4 (10%)
T-cell depletion	Ex vivo	8 (20%)
	Serotherapy: Campath	10 (25%)
	Serotherapy: ATG	15 (38%)
	None	7 (18%)

Data are n patients (%).
Allo-HSCT, allogeneic hematopoietic stem cell transplant; ATG, anti-thymocyte globulin.

BCV Exposure

- Patients received a median of 24 (Interquartile range [IQR]: 17-34) BCV doses over a median of 82 (59-130) days.

Virologic Responses

- AdV became undetectable during BCV treatment in 32 (85%) patients (**Table 3**).
- AdV viremia decreased quickly on BCV treatment for a number of patients, with a median (IQR) time to first undetectable being 22 (15-38) days.

Table 3. AdV viremia outcomes

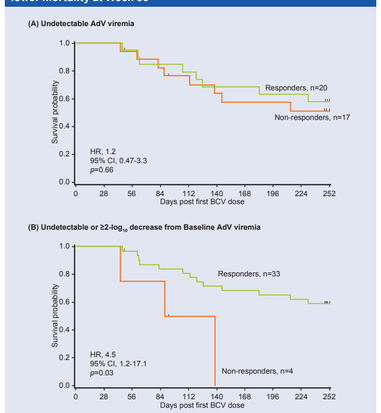
		(n=40)
Undetectable	At any time on treatment	34 (85%)
	Week 4	20 (50%)
	Week 6	22 (55%)
Undetectable or ≥2 $\log_{10}$ copies/mL decrease from Baseline	At any time on treatment	36 (90%)
	Week 4	33 (83%)
	Week 6	27 (68%)
Time to first undetectable (days)	Median (IQR)	22 (15-38)
Days undetectable[†]	12-week median (IQR)	43 (15-63)
Time <1000 copies/mL (days)[†]	12-week median (IQR)	66 (40-77)
Area Under the viremia-time Curve (AUC, $\log_{10}$ copies/mL*days)	12-week mean (SD)	193 (85)
Time-averaged AUC (AAUC, $\log_{10}$ copies/mL)	12-week mean (SD)	2.9 (1.3)

Data are n patients (%), unless otherwise stated.
[†]Time period considered as below threshold if 2 consecutive readings below threshold. Imputed as detectable/≥1000 for time after death or lost to follow-up.
AdV, adenovirus; IQR, interquartile range; SD, standard deviation.

Clinical Outcomes and Correlation With Virologic Responses

- 38/40 (95%) patients completed follow-up to Week 36. Twenty-one (53%) patients survived, while 19 (47%) died.
- Significantly lower mortality was observed among patients who had achieved an undetectable or ≥2 $\log_{10}$ decrease in AdV viremia from Baseline at Week 4, but not among those who had achieved clearance of AdV viremia (i.e., undetectable AdV viremia; **Figure 1**).

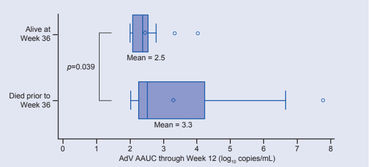
Figure 1. Virologic response at Week 4 was associated with lower mortality at Week 36



AdV, adenovirus; CI, confidence interval; HR, hazard ratio.

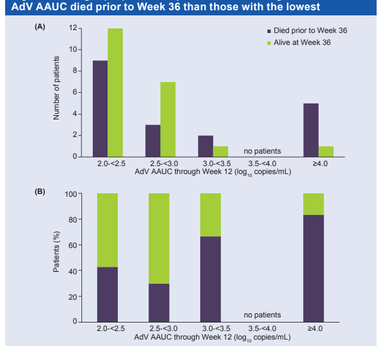
- Mean AdV viral burden (measured by AdV AAUC) over the 12 weeks post first BCV dose was associated with survival to Week 36.
  - Mean (SD) AdV AAUC was 2.5 (0.5) $\log_{10}$ copies/mL in patients alive at Week 36 versus 3.3 (1.7) $\log_{10}$ copies/mL in patients who died prior to this time point (**Figure 2**; $p=0.039$).
- Over 80% of patients with 12-week AdV AAUC values ≥4.0 $\log_{10}$ copies/mL had died by Week 36, as compared with <40% of those with values <3.0 $\log_{10}$ copies/mL (**Figure 3**).
- Patients with the highest 12-week AdV AAUC (≥4.0 $\log_{10}$ copies/mL), were least likely to survive to Week 36 (**Figure 4**).
- Baseline AdV viremia was correlated with 12-week AdV AAUC (R^2=0.30, p=0.0002), indicating that early treatment (i.e., at lower viral loads) could lead to a decreased viral burden.

Figure 2. Significant association between lower AdV AAUC and survival at Week 36



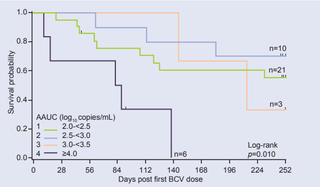
Data are presented as mean (diamond); median (center-line); interquartile range (box); most extreme value within 1.5x interquartile range of quartile 1 and 3 (whiskers), and the individual points that fall outside this (circles). Statistical comparison by Satterthwaite *t*-test.
AAUC, time-averaged area under the viremia-time curve; AdV, adenovirus.

Figure 3. A larger proportion of patients with the highest 12-week AdV AAUC died prior to Week 36 than those with the lowest



AAUC, time-averaged area under the viremia-time curve; AdV, adenovirus.

Figure 4. Kaplan-Meier survival to Week 36 was poorest in patients with the highest 12-week AdV AAUC



AAUC, time-averaged area under the viremia-time curve; AdV, adenovirus.

CONCLUSIONS

- **In pediatric allo-HSCT recipients with clinically relevant AdV viremia (≥1000 copies/mL), treatment with BCV was associated with a rapid plasma virologic response and reductions in overall AdV viral burden.**
- **Rapid virologic response at Week 4 was associated with improved survival.**
- **The significant association observed between lower AdV AAUC and survival at Week 36 suggests that AAUC is an appropriate measure to assess the potential benefits of antiviral therapies in pediatric allo-HSCT recipients.**

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DISCLOSURES

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TB, EV, GC, and GN are employees of and hold stock in Chimerix.

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