Antiviral Toxicities Among Pediatric Solid Organ Transplant Recipients

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Background

- Ganciclovir (GCV) and valganciclovir (VGCV) are used for prophylaxis (PPX) and treatment for CMV infection in pediatric solid organ transplant (SOT) recipients.
- Hematologic and kidney-related adverse events are common among recipients of these medications, but the frequency and severity of these events in the first year post-transplant are not well described.
- Children's Hospital of Philadelphia (CHOP) provides CMV prophylaxis (PPX) with valganciclovir to all high (D+/R-) and medium risk (R+) SOT recipients:
  - 3 months for heart and liver, 6 months for kidney, 12 months for lung.

Objectives

- To describe the epidemiology of potential antiviral toxicities (acute kidney injury [AKI], neutropenia, leukopenia, thrombocytopenia) in SOT recipients at CHOP within the first year of SOT.
- To evaluate provider management in relation to identification of potential antiviral toxicities over the first year following transplant.

Methods

Study Design & Population: Retrospective cohort study of all children (<19 years old) undergoing SOT at CHOP from January 2012 – June 2018. Data were abstracted from the EMR and reviewed to identify laboratory-based toxicities between 15 days and 1 year post-transplant. Date of onset and of most abnormal value(s) were collected. Medication management and need for hospitalization within 14 days of toxicity onset was recorded.

Inclusion criteria: a) Transplanted at CHOP; b) Age <19 years at transplant; c) Toxicity occurring >14 days following transplant. *Exclusion*: Transferred care to another institution following SOT (data included up to time of transfer).

Definitions:

GCV or VGCV-associated toxicity: patient was receiving an antiviral at onset of laboratory-based adverse event

Acute kidney injury: ≥50% change in serum creatinine (SCr) from 30 days prior (KDIGO criteria). SCr changes must have occurred within 7 days and value must be ≥0.5 mg/dL on day of AKI. AKI severity based on maximal SCr change from baseline: stage I = 50 – <100%, stage II = 100 - <200%, stage 3 = ≥200%

Leukopenia: white blood cell count < 3500/μL

Neutropenia: absolute neutrophil count <1000/μL; severe neutropenia: < 500 /μL

Thrombocytopenia: platelet count < 100,000/μL

Onset and resolution of toxicity: Hematologic toxicity episodes defined as ≥2 consecutive abnormal measurements. Resolution defined as 2 consecutive normal measurements or >2 weeks between abnormal measurements with a single normal measurement in between. Resolution of AKI episode defined as 2 consecutive SCr measurements that did not qualify as AKI.

Analysis: Incidence rate of toxicities (episodes per 1000 follow-up days) were calculated based on receipt of VGCV or GCV as PPX or treatment, or no antiviral. Comparison of incidence rate ratios (IRR) for toxicities during VGCV and GCV vs no antiviral were performed using univariate Poisson regression in STATA 15.1 (StataCorp LLC, College Station, TX).

Results

- **The study population included 285 children who received 299 SOTs**

Table 1. Characteristics of the study population

Variable	Number (n = 299)
Gender, n (%)	
Female	175 (58.3)
Male	124 (41.5)
Age at transplant, median (IQR)	6.5 (2.0-12.8)
Race, n (%)	
Asian	8 (2.7)
Black/African-American	55 (18.4)
White	165 (55.2)
Other/More than one race	71 (23.7)
Hispanic ethnicity, n(%)	49 (16.4)
Organ transplanted, n(%)	
Heart	69 (23.1)
Kidney	91 (30.4)
Liver	108 (36.1)
Lung	31 (10.4)
CMV status, n(%)	
D+/R- (high risk)	110 (36.8)
D+/R+ or D-/R+ (medium risk)	94 (31.4)
D-/R- (low risk)	95 (31.8)

2 transplants with D unknown/R+ and 1 D-/R unknown considered medium risk; 3 D+/R unknown considered high risk.

- **A total of 561 laboratory-based adverse events were identified**
  - Nearly half (46.4%) of toxicity episodes occurred while SOT recipients were on GCV or VGCV PPX or treatment.
  - VGCV or GCV were administered on only 23% of all follow-up days.

- **Antiviral-associated AKI: 66 episodes**
  Severity: stage I - 11 (17%), stage II – 32 (48%), stage III - 23 (35%)

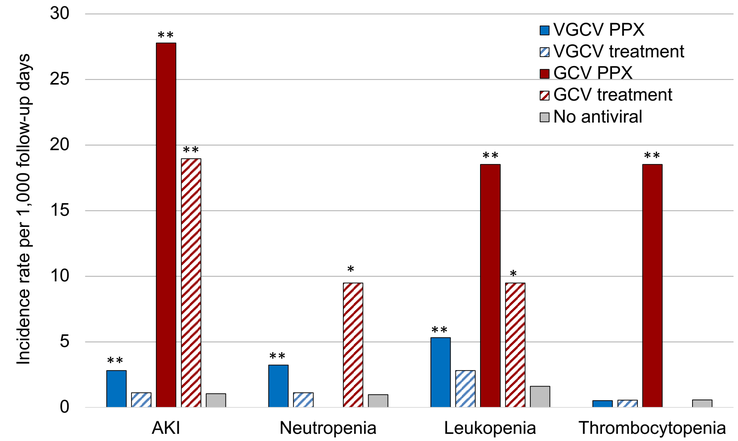
- **Antiviral-associated neutropenia: 66 episodes**
  Severity: moderate - 23 (35%), severe - 43 (65%)

Table 2. SOT recipients with toxicities during antiviral PPX or treatment

Variable	VGCV PPX (n = 166)	VGCV treatment (n = 29)	GCV PPX (n = 23)	GCV treatment (n = 9)
Any toxicity, n (%)	106 (63.9)	7 (24.1)	7 (30.4)	4 (44.4)
AKI, n (%)	31 (18.7)	2 (6.9)	3 (13.0)	2 (22.2)
Leukopenia, n (%)	82 (49.4)	5 (17.4)	4 (17.4)	2 (22.2)
Neutropenia, n (%)	49 (29.5)	2 (6.9)	0	2 (22.2)
Thrombocytopenia, n (%)	8 (4.8)	1 (3.5)	3 (13.0)	0

Numbers and proportions displayed represent patients who experienced antiviral toxicities at any time while patient was receiving that agent for that indication (PPX or treatment).

Figure 1. Incidence rate of toxicities from day 15 through 1 year post-transplant.



Comparisons for IRR of toxicities during VGCV and GCV PPX or treatment versus no treatment.
*Signifies IRR greater than 1 with p-value <.05. ** Signifies IRR greater than 1 with p-value <.001.

Table 3. Management of antiviral toxicities

Variable	AKI (n = 66)	Neutropenia (n = 66)
Stoppage or dose adjustment of:		
Antiviral	30 (45%)	43 (65%)
TMP/SMX PPX	2 (4%)	23 (35%)
Immunosuppression	31 (57%)	23 (35%)
Antiviral and immunosuppression	22 (33%)	19 (29%)
Antiviral, TMP/SMX and immunosuppression	2 (4%)	13 (20%)
Hospitalization	6 (9%)	7 (11%)

Conclusions

- Significant hematologic and kidney-related toxicities occurred in pediatric SOT recipients receiving GCV and VGCV for CMV PPX and treatment at our hospital.
- Although we cannot ascribe causality to laboratory-based adverse events, they were more common in SOT recipients receiving these antivirals.
- Future work will evaluate antiviral toxicities in the context of other potential causes (concurrent medications, infections) using multivariable analytic techniques.
- While VGCV and GCV are effective at preventing CMV disease in pediatric SOT, clinicians should consider risk of toxicity when evaluating CMV prevention strategies.

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