Combination antiviral CMV therapy with ganciclovir and foscarnet in high risk infants

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Abstract

Background: Newborn screening for immune deficiencies including severe combined immunodeficiency (SCID) is being implemented nationwide, knowing that hematopoietic stem cell transplantation dramatically improves survival. A major risk factor in these infants is CMV infection, which decreases transplant success. Specific antiviral therapy must be early and aggressive because of the potential for resistance and rapid dissemination. Combination antiviral therapy is routine for some viral infections such as HIV, but the value of this approach for CMV is unclear.
Methods: Medical records of infants ≤ 6 months (M) of age hospitalized between 2007-2015 who received ganciclovir (GCV) or foscarnet (FOS) monotherapy or combination GCV + FOS for CMV disease, with viral loads followed, were studied. Patients receiving prophylaxis only were excluded. Viral load data, absolute neutrophil and platelet counts, serum creatinine, electrolytes, and results of CMV resistance testing, if performed, were reviewed.
Results: Five children (mean, 2.5 M; range, 2-3.4 M) received initial combination GCV + FOS while 25 children (mean age 2.8 M; range,1.3-6.0 M) received either GCV or FOS monotherapy. Median initial and peak viral loads were higher in the combination therapy group and these patients all demonstrated initial improvement in viral loads. Three of four who continued treatment recovered. Toxicity was common in both groups; neutropenia, thrombocytopenia and electrolyte abnormalities occurred most frequently. Resistance testing was not routinely performed in children receiving monotherapy, but 3 of 4 infants in the GCV+FOS group did have testing; no mutations were detected.
Conclusions: Combination GCV + FOS therapy may be an effective alternative to monotherapy with GCV or FOS alone in high-risk infants, especially in those with primary immune deficiencies. Although our findings are limited by small numbers at a single center, toxicity from mono- and combination therapy was comparable. Despite protracted infections and high viral loads in high-risk infants receiving GCV+FOS, clear CMV resistance was not detected. Although the numbers treated with combination therapy is too small to assess the impact on the development of resistance or overall survival, this approach should be studied further.

Introduction

- Premature and immunocompromised infants are at high risk for severe CMV.
- CMV and other viral infections can delay HSCT and reduce long-term survival in infants with severe immune deficiencies.
- Treatment options for CMV are limited by toxicity and resistance:
  - GCV: myelosuppression and nephrotoxicity
  - FOS: electrolyte abnormalities and nephrotoxicity
- For a number of viral infections, combination therapy is the standard of care; whether this advantage applies to herpes viruses is unclear [Drew 2006].
- In vitro data indicate that GCV and FOS may be somewhat synergistic [Cai et al, Manischewitz et al]. In vivo data is limited.
- Many experts currently switch to combination therapy when monotherapy fails. Using both agents initially has not been optimally studied.
- In response to a series of young infants with severe CMV disease who developed GCV resistance, we developed an aggressive initial combination therapy (GCV + FOS) approach for certain high-risk infants.

Methods

Medical records of infants < 6 months who received GCV or FOS alone (monotherapy group), or in combination for CMV disease, and who had viral load data available at SCH were reviewed for the time period 2007-2015. Infants receiving CMV prophylaxis only were excluded.

Combination therapy was defined as both GCV + FOS at or soon after (<14 days) the time of diagnosis with CMV infection. Toxicities were measured during the time that combination therapy was administered. Subsequent monotherapy periods were included in that group if new toxicities developed. Those infants who received dual therapy later in their courses were included in the monotherapy group only.

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Conflicts of interest: JE and SV were sub-investigators for Chimerix brincidofovir study

Patient Characteristics

	Monotherapy Group (n=25)	Dual Therapy group (n=5)
Gender	38% Female	40% Female
Ave Gest Age (weeks)	34.6	36.0
Underlying Diagnosis	6 (24%) prematurity 8 (32%) SOT 1 (8%) CHD 4 (16%) immune deficiency 2 (8%) congenital CMV 4 (16%) other	40% SCID 20% T cell immunodefiency 20% HLH 20% prematurity
Ave Age at CMV Diagnosis (mos)	2.8	2.5
Median Viral load at diagnosis (IU/mL)	885	35,000
Median Peak Viral load (IU/mL)	1,962	1,625,000
CMV sequelae	6 (24%) respiratory 4 (16%) thrombocytopenia 4 (16%) hepatitis 4 (16%) hearing loss/CNS 2 (8%) myocarditis	4 (80%) respiratory 1 (20%) hepatitis
Age at BMT (months)	N/A	5.5 (n=2)

SOT= solid organ transplant
CHD= congenital heart disease
HLH = hemophagocytic lymphohistiocytosis

Toxicity

	Thrombocyto-penia (<100)	Neutropenia (<500)	Creatinine elevation (≥0.3 rise)	Electrolyte abnormality requiring correction (K,Ca,Mg,Phos)***	Mortality (<90 days of CMV diagnosis)
Monotherapy Group (GCV) N= 29*	12 (41%)	12 (41%)	2 (7%)	12 (41%)	4 (16%) n=25
Dual Therapy Group (n=5)	3 (60%)	2 (40%)	2 (40%)	3 (60%)	1 (20%) n-=4**

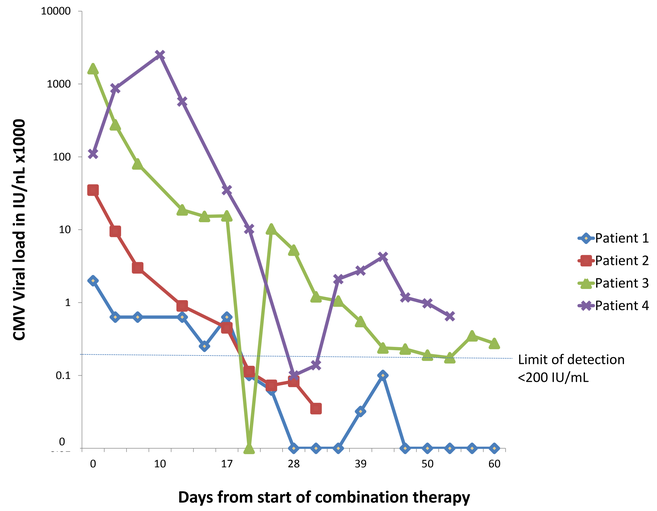
*1 patient had 2 courses in monotherapy group, 3 combination therapy infants subsequently had courses of monotherapy
**1 combination patient transitioned to palliative care (toxicity results during combo tx included)
***Electrolyte abnormalities were defined as follows: potassium <3.2 mg/dL, phosphorus <3.8 mg/dL or >6.5 mg/dL, magnesium <1.6mg/dL or ionized calcium < 1.15 mmol/L.

Resistance

	Testing obtained	Mutations found
Monotherapy Group (GCV) n= 25	1 (6%)	1: UL97/M615V**
Dual Therapy Group n=4	3 (75%)	1: UL97:D605E*

*UL97, D605E interpretation: In vitro experiments have shown normal phosphorylation function of the UL97 gene when the D605E mutation is present [Chou et al 2002] and D605E polymorphism was found frequently in patients not exposed to GCV (Tanaka et al 2011]. This mutation was also found frequently in transplant patients [Zhou et al 2006] and was conjectured by those authors to be a natural sequence variant. One reported case had this mutation prior to the development of drug resistance (Puch et al, 2004]. A strong association of the D605E mutation with CMV drug resistance has not been conclusively established.
** M615V also not an established GCV resistance causing mutation [Chou 2015] but has been found in pediatric SOT patients exposed to valgancyclovir prophylaxis [Martin et al 2010].

Viral load response in GCV+FOS patients



Discussion

- In the GCV+FOS group, adverse events were frequent but mild and similar to those seen in the monotherapy group. Myelosuppression, electrolyte abnormalities and renal dysfunction were generally reversible.
- Monotherapy patients rarely had resistance testing sent.
- In combination patients only 1 UL97 mutation was found, of unclear clinical significance. No UL54 mutations were found.
- A study of CMV in SCID patients noted early resistance (1.5-3 weeks) with UL97 gene mutations [Wolf et al 1998].
- YJ Kim et al (2012) found UL97 mutations in five children with underlying immunodeficiency and CMV following HSCT and SOT. The viral loads were high and disease was severe, requiring prolonged therapy. Two of these patients died from as a result of CMV infection.
- This propensity toward the development of resistance may suggest that an alternate approach such as combination antiviral therapy is warranted in patients with immunosuppression and high viral loads, especially those bound for HSCT.

Limitations

This is a retrospective review with a small number of patients which can not establish any causality
Our combination therapy group had more severe CMV disease due to their underlying conditions. This is evidenced by their higher initial and peak viral loads. Therefore a direct comparison can not be made between dual and monotherapy.

Conclusions

- Immune deficient infants are at high risk for complicated and severe CMV infection which can result in resistance, delayed HSCT and mortality
- Toxicity, while present in both therapy groups, seemed tolerable even with the use of both agents
- Resistance testing should be considered early in high-risk patients on prolonged treatment courses of antiviral therapy
- Antiviral resistance was infrequent in the combination therapy group
- Combination antiviral therapy with FOS and GCV is a strategy worth studying further in very high-risk infants