Cytomegalovirus in Pediatric Hematopoietic Stem Cell Transplantation: A Case-Based Panel Discussion of Current Challenges

Lara Danziger-Isakov,1 Janet Englund,2 Michael Green,3 Klara M. Posfay-Barbe,4 and Danielle M. Zerr2

1Division of Infectious Diseases, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Ohio; 2Division of Infectious Diseases, Department of Pediatrics, Seattle Children's Hospital, Washington; 3Division of Infectious Diseases, Department of Pediatrics, Children's Hospital Pittsburgh, Pennsylvania; and 4Division of Infectious Diseases, Department of Pediatrics, Children's Hospital of Geneva, University Hospitals of Geneva, Switzerland

Cytomegalovirus (CMV) remains a significant contributor to morbidity and death after pediatric solid and stem cell transplantation. Decisions regarding prevention and treatment often lack pediatric-specific data to drive decision making. We present here a case-based discussion around some of these specific topics and focus on approaches to CMV prevention, post-CMV secondary prophylaxis options, and identification and treatment of resistant CMV infection, including emerging antiviral agents and the use of cytotoxic CMV-specific T-cells, in the setting of pediatric hematopoietic stem cell transplantation.

A 10-year-old boy with chronic granulomatous disease who is cytomegalovirus (CMV) seropositive without history of a documented CMV-related illness presents for match-unrelated donor hematopoietic stem cell transplantation (HSCT). What type of CMV monitoring and prevention strategies will you use for this patient?

The decision around what CMV prevention strategy to use on a pediatric patient depends on several factors, because options exist for either prophylactic antiviral therapy or preemptive monitoring. Preemptive monitoring would result in the use of antiviral agents only if CMV is detected. When deciding whether prophylaxis or preemptive monitoring and therapy are preferable, the risk for CMV disease needs to be balanced by the complications related to antiviral prophylaxis. First, this patient is at risk for CMV infection because of his CMV-seropositive status. If he and his donor both had been seronegative, the CMV risk would have been substantially lower and would not have favored prophylaxis. Second, he did not have a pre-HSCT CMV event. Pre-HSCT CMV DNAemia is associated with an increased risk for post-HSCT CMV and suggests that prophylaxis might be preferred in this population [1]. Next, consideration for the effect of antiviral therapy on engraftment should be considered.

Ganciclovir and valganciclovir are associated with bone marrow toxicity, including leukopenia and neutropenia. Administration of these agents during the preengraftment period can increase the duration of post-HSCT neutropenia. Alternative prophylactic medications, such as foscarnet and cidofovir, are available but have additional toxicities, including nephrotoxicity and electrolyte disturbances, which temper enthusiasm for providing these medications universally. Although a novel CMV-directed antiviral that has no known hematologic or renal toxicities, letermovir, was recently approved for the prevention of CMV in adult HSCT recipients [2], information on pediatric dosing, safety, and efficacy is not yet available. Therefore, after balancing the potential risks and benefits of the options, the panel supports serial monitoring and preemptive antiviral therapy for this patient.

Forty days after the transplant, the patient was found to have a CMV viral load of 150 000 IU/mL. He was treated successfully with ganciclovir, which cleared his viral load, and he has remained on valganciclovir prophylaxis after this event. One hundred days after the transplant, his CMV viral load again is elevated (60 000 IU/mL). He has poor engraftment. What treatment should be used for this child who is already on valganciclovir prophylaxis?

With the recurrence of a significant CMV viral load while still receiving valganciclovir prophylaxis and the notation of poor engraftment, the panel chose to initiate foscarnet therapy at this juncture. The information about poor engraftment tipped the decision toward foscarnet because of concerns for persistent bone marrow toxicity with additional valganciclovir or ganciclovir treatment and prophylaxis. If the patient had had substantive graft-versus-host disease (GVHD) that limited oral absorption and it was determined that the oral valganciclovir was not being absorbed, 2 options could have been considered. One option would be to transition him to intravenous ganciclovir and continued monitoring of his CMV load. The second option would be to monitor his blood ganciclovir levels to assess his level of absorption. However, because ganciclovir measurements are not routinely available at many institutions and this patient did not have GVHD of the bowel at the time, foscarnet was again preferred by the panel.
The patient was started on foscarnet, and after 7 days of therapy, his CMV viral load has increased to 180,000 IU/mL. Do you perform resistance testing at this time?

Because of the viral kinetics of CMV, which has a doubling time of approximately 48 hours, it is conceivable that the viral load might not substantially decrease, and might in fact increase, in the first week of adequate therapy. In addition, differences of up to a ½-log change in viral load might be associated with the assay itself [3]. CMV resistance is rare after pediatric HSCT (10% of CMV episodes in 1 study [4]). Solid organ transplantation guidelines [5] recommend that drug resistance be suspected and testing conducted in patients with a previous cumulative exposure to (val)ganciclovir of more than 6 weeks, breakthrough CMV infection while on prophylaxis, and clinical treatment failure despite at least 2 weeks of antiviral therapy. Seven days into therapy, resistance testing would not be suggested initially. However, after an additional week of therapy, our patient's viral load remained unchanged, and so resistance testing was ordered.

Resistance testing revealed mutations in both UL97 and UL54, which confer resistance to both ganciclovir and foscarnet. What additional options exist for this patient?

With the emergence of resistance to both ganciclovir and foscarnet, treatment options for this patient are limited but have not been exhausted. Careful assessment of the resistance testing should be performed to evaluate if the potential for cross-resistance to other antivirals exists, which can occur in the CMV UL54 polymerase mutations. If these mutations do not exist, therapy with cidofovir can be considered, while appreciating the risk for nephrotoxicity with administration of this medication. Brincidofovir, a lipid-conjugated prodrug of cidofovir that does not result in any known associated nephrotoxicity and is not currently approved for any clinical use, could be considered if it were released for compassionate use by the parent company. However, no specific studies of this medication addressed its efficacy for resistant CMV disease, and its efficacy in the treatment or prevention of CMV has not been established in clinical trials. Resistance testing for our patient revealed a cross-reactive UL54 mutation conferring resistance to (br)cidofovir.

Other antiviral options have been reported in the literature, mostly for adult solid organ transplant recipients. Reports of case series of patients treated with both leflunomide [6] and maribavir [7] have shown successful treatment of resistant CMV with these antivirals. Maribavir has not approved by the Food and Drug Administration (FDA), is no longer available for compassionate use, and currently is available only for children aged 12 years or older through enrollment in an ongoing study that is evaluating the use of maribavir specifically for resistant and refractory CMV infections in transplant recipients (ClinicalTrials.gov identifier NCT01611974). Off-label use of letermovir, a novel agent that inhibits the CMV terminase complex (UL56) that cleaves and packages virus and was recently approved by the FDA for adult HSCT recipients for CMV prophylaxis, could be considered. One published report describes an adult lung transplant recipient who was treated successfully with letermovir for resistant CMV [8]. However, its dosing, safety, and efficacy in pediatric patients have not yet been determined, which complicates the potential use of this agent in our population. Last, infusion of CMV-specific cytotoxic T lymphocytes (CTLs) could be considered. With poor engraftment and persistent DNAemia, it could be inferred that our patient has an absence or functional deficit in his own CMV-specific CTLs. Generation of CTLs from a variety of sources, including virus-naïve or virus-experienced autologous or allogeneic sources, including partially HLA-matched third-party donors, has been reported [9] and used in CMV prevention and treatment for HSCT recipients. However, these cells are not routinely available at many centers, and a commercial product is not yet approved, which limits their accessibility in direct patient care at this time.

For our patient, maribavir was not available for compassionate use. Letermovir was not approved by the FDA at the time of his illness and was therefore unavailable. Resistance testing revealed a mixed population of both wild-type and resistant viruses, which prompted the continuation of both ganciclovir and foscarnet. In addition, haploidentical CMV-specific CTLs derived from the patient’s mother were administered on 2 occasions without a significant clinical response.

CONCLUSION

The treatment of recurring, relapsing, or resistant CMV in transplant recipients can be difficult and lead to serious problems after the transplant. The patient discussed here subsequently experienced progressive respiratory failure, and he later died as a result of bacterial sepsis and multiorgan system failure. Treatment options for pediatric patients with difficult-to-treat CMV disease are limited at this time, and it is hoped that several of the newer agents and modalities of therapy will be available for patients in this age group in the near future.

Note

Supplement sponsorship. This supplement was sponsored by St. Jude Children’s Research Hospital, Memphis, Tennessee.

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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CMV in Pediatric HSCT • JPIDS 2018:7 (Suppl 2) • S73


