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Review Article

Evaluation and treatment of post-renal transplant cytomegalovirus disease in children

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ABSTRACT

Cytomegalovirus (CMV) infection typically presents as viremia, a clinical syndrome, or tissue-invasive disease. Identifying risk factors and conducting initial blood investigations, followed by invasive tests when appropriate, are crucial steps to rule out serious tissue-invasive disease. Ganciclovir is the cornerstone of CMV disease treatment, with oral valganciclovir used subsequently based on treatment response. For patients with UL-97 mutant ganciclovir-resistant CMV, foscarnet may be administered, often alongside intravenous immunoglobulin (IVIG), particularly in cases of life-threatening conditions such as CMV pneumonitis. Despite the significance of CMV in this population, there is currently a lack of comprehensive clinical reviews or guidelines specifically addressing the management of post-renal transplant CMV disease in children. This article aims to fill that gap by discussing the various modalities for treating post-renal transplant CMV in children, along with its clinical manifestations and necessary investigations.

Keywords: Cytomegalovirus, IVIG, ATG, CCT

INTRODUCTION

Cytomegalovirus (CMV) is a common virus that can cause significant complications, particularly in immunocompromised individuals. It's crucial to differentiate between CMV infection and CMV disease, as their management strategies differ.[1-3]

DEFINITIONS

CMV infection is defined by the presence of CMV replication, irrespective of whether symptoms are present. It can be identified through several findings. These include seroconversion, marked by the appearance of anti-CMV IgM antibodies, or a fourfold increase in pre-existing anti-CMV IgG titres. The presence of CMV can also be detected via a CMV antigenemia assay (pp65), or through the detection of CMV-DNAemia or CMV-RNAemia using molecular techniques. Furthermore, isolation of the virus through culture of throat, buffy coat, or urine samples (indicating CMV viremia) confirms infection.[1,2,4-6]

CMV disease occurs when CMV infection is accompanied by noticeable clinical signs and symptoms. This can manifest as CMV Syndrome, which typically involves fever and/or malaise, along with leukopenia and thrombocytopenia. More severe presentations fall under Tissue-invasive CMV disease, affecting specific organs. Examples include hepatitis, pneumonitis, pancreatitis, colitis, meningoencephalitis, chorioretinitis, and myocarditis.[6,7]

RISK FACTORS

Several factors increase an individual's susceptibility to CMV infection and disease. A significant risk is the donor

CMV seropositive-recipient-seronegative (D+/R-) state, where a CMV-exposed donor transmits the virus to a recipient who has no prior immunity. Prolonged cold ischemia time in transplantation also heightens the risk. Immunosuppression plays a critical role, particularly the use of lymphocyte-depleting agents such as antithymocyte globulin (ATG), which can lead to leukopenia and lymphopenia, further increasing vulnerability. The presence of other concurrent infections, such as bacteraemia, invasive fungal disease, and Epstein-Barr virus-associated post-transplant lymphoproliferative disorder, can also predispose individuals to CMV. It is also important to consider CMV infection as a potential cause in cases of chronic allograft nephropathy of unexplained origin. [8-10]

LABORATORY INVESTIGATIONS FOR DIAGNOSIS

Diagnosing CMV infection and disease relies on a range of laboratory investigations.

CMV serology has limited utility in diagnosing active CMV infection in immunosuppressed patients due to their compromised ability to mount an antibody response. Viral culture, typically from blood (buffy coat), is another method but its turnaround time is often too slow for timely clinical decision-making.[8-11]

The CMV antigenemia assay, specifically detecting the pp65 antigen, offers good sensitivity but its utility is restricted in leukopenia patients. Molecular tests are widely used, performed via semiquantitative polymerase chain reaction (PCR) or quantitative nucleic acid testing (QNAT) assays. CMV quantitation provides information on viral load; for instance, a high CMV viral load (defined as over 1000 copies/µg DNA at the Paediatric Renal and Transplant Immunology laboratory in Singapore) can be indicative of significant infection. Lower viral loads are often observed with asymptomatic CMV infection. It is worth noting that a minority of patients may present with low CMV viral loads despite having tissue-invasive disease, due to CMV compartmentalization. The detection of CMV RNAs is indicative of active CMV replication. Finally, a renal biopsy can be a crucial tool, helping to differentiate tissue-invasive CMV disease from concurrent graft rejection.[11-13]

EVALUATING TISSUE-INVASIVE DISEASE

When assessing for tissue-invasive CMV disease, a comprehensive set of laboratory and imaging evaluations is undertaken. These include a full blood count, which provides an overview of blood cell components. Inflammatory markers such as sedimentation rate and C-reactive protein are also measured. Liver function is assessed through tests for albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), and bilirubin. Renal function is evaluated by checking urea and creatinine levels. A chest radiograph can help identify pulmonary involvement, and an ophthalmology screen is important for detecting chorioretinitis.[8,9,11]

TREATMENT OF CMV DISEASE

The primary antiviral agent for CMV disease is ganciclovir. Treatment typically begins with daily intravenous ganciclovir administered at a full dose for two to three weeks, adjusted according to renal function. This initial phase continues until clinical symptoms resolve, with the exact duration varying based on clinical response, other relevant parameters, and the presence of adverse effects such as neutropenia. Following this, oral valganciclovir is used at treatment doses, the choice of which depends on the patient's response. This phase continues until at least two consecutive weekly CMV PCR results are negative. The risk of CMV relapse is lower when the CMV viral load is undetectable or falls below a specific negative threshold for the given test. The total treatment duration should be at least three months, especially if there's a high risk for recurrence, such as in cases of donor-seropositive to recipient-seronegative status or when anti-thymocyte globulin has been used. After the treatment course is completed, a secondary prophylaxis with oral valganciclovir should be continued for an additional three months.[11-13]

DOSING REGIMENS

Specific dosing regimens for ganciclovir and valganciclovir are crucial for effective treatment.

Intravenous ganciclovir dosing

For intravenous ganciclovir, the dose is adjusted based on creatinine clearance (CCT) in ml/min/1.73 m²: CCT >70: 5 mg/kg/dose every 12 hours, CCT 50-69: 2.5 mg/kg/dose every 12 hours, CCT 25-49: 2.5 mg/kg/dose every 24 hours, CCT 10-24: 1.25 mg/kg/dose every 24 hours and CCT <10 or on haemodialysis (HD): 1.25 mg/kg/dose three times per week (administered after HD).[7,8,10,11,13]

Oral valganciclovir dosing

Valganciclovir has a maximum dose of 900 mg, with each capsule containing 450 mg. For transplantation patients, the treatment dose for adults and paediatrics is as follows, based on CCT (ml/min/1.73 m²): CCT >60:900 mg four times daily, CCT 40-59: 900 mg every other day, CCT 25-39:450 mg every other day, CCT 10-24: 450 mg twice weekly and CCT<10: Not recommended for patients undergoing haemodialysis.[7,8,10,11,13,14]

Alternatively, for paediatric dosing equivalent to a 900 mg dose, the calculation is 900/125 multiplied by the body surface area (BSA) and the glomerular filtration rate (GFR in ml/min/1.73 m²), which simplifies to 720×BSA×GFR (ml/min/1.73 m²), as described by Ettenger et al.

MANAGING ADVERSE EFFECTS AND RESISTANCE

If adverse effects occur, the ganciclovir dose may be halved as a single daily dose, administered for a minimum of five days per week. For patients with renal impairment, this might translate to an every-other-day dose for the full dose. Thrombocytopenia, specifically a platelet counts below 100×10^9/L, warrants close monitoring. If the thrombocytopenia is determined to be drug-related, a dose reduction should be considered.[7,8,10,11,13,15]

Treatment should be discontinued if the total white cell count drops below 0.3×10^9/L or if neutropenia occurs, defined as an absolute neutrophil count below 1.0×10^9/L. Therapy can be resumed at the previous dose, or at an every-other-day dose, once the absolute neutrophil count rises to 1.5×10^9/L or higher. If the absolute neutrophil count remains low, administering granulocyte-colony stimulating factor (GCSF) may be considered.

Ganciclovir resistance is suspected when the viral load increases or remains unchanged after two weeks of adequate ganciclovir dosing. In such cases, testing for UL97/UL54 mutations is recommended. Strategies to manage resistance include doubling the intravenous ganciclovir dose (e.g., 10 mg/kg twice daily for normal renal function) or switching to intravenous foscarnet if the CMV disease is severe or if UL97 ganciclovir resistance is confirmed.

FOSCARNET AS A SECOND-LINE TREATMENT

Foscarnet serves as a second-line treatment, particularly for UL-97 mutant ganciclovir-resistant CMV. The induction treatment involves 180 mg/kg/day, divided into doses given every 8 or 12 hours, for a period of 14 to 21 days. Maintenance therapy typically consists of 90-120 mg/kg/day as a single daily infusion.[11,12,14,15]

PRECAUTIONS WITH FOSCARNET USE

Caution is advised when using foscarnet in patients with renal impairment, altered electrolyte levels, or pre-existing neurological or cardiac abnormalities. The dose must be adjusted for individuals with impaired renal function.

Treatment should be discontinued if the serum creatinine reaches or exceeds 250 µmol/L and can be restarted if the serum creatinine falls to 180 µmol/L or less. Foscarnet is a known venous irritant, necessitating infusion only into veins with adequate blood flow. Maintaining adequate hydration can help reduce the risk of nephrotoxicity.

Several drug interactions should be considered: pentamidine can lead to additive hypocalcaemia; cyclosporine, aminoglycosides, and amphotericin B can cause additive nephrotoxicity; and ciprofloxacin may increase the potential for seizures.[11,13,15]

INTRAVENOUS IMMUNOGLOBULIN (IVIG)

Intravenous immunoglobulin (IVIG) should be administered in specific clinical scenarios. These include tissue-invasive CMV disease, life-threatening conditions like CMV pneumonitis, and in cases of hypogammaglobulinemia. CMV hyperimmune globulin is generally preferred when available.[5-7,9,10]

The administration schedule involves daily doses for one week, followed by alternate-day administration for two weeks or until clinical symptoms subside. This is then followed by twice-weekly doses for two weeks, then weekly for one month, and subsequently every other week for one month, concluding with monthly doses for two to three months. The total treatment duration typically ranges from four to six months, depending on the clinical severity and treatment response.

DECREASING IMMUNOSUPPRESSION

A crucial aspect of managing post-renal transplant CMV disease in children involves judiciously decreasing immunosuppression. This typically includes reducing or discontinuing anti-metabolites such as azathioprine or mycophenolate mofetil. If there's a high risk of rejection, changing mycophenolate to everolimus may be considered. Prednisolone and calcineurin inhibitors should generally be continued unless there is clear evidence of a life-threatening infection.[7,9,11]

MONITORING DURING TREATMENT

Regular monitoring is essential throughout CMV therapy. CMV PCR should be performed weekly until two consecutive negative tests are achieved, then fortnightly for one month, and subsequently monthly for six months. During intravenous ganciclovir therapy, weekly monitoring should also include a full blood count, liver panel, and renal function tests. For cases of CMV pneumonitis, the diffusing capacity of the lungs for carbon monoxide (DLCO) should be monitored, with improvements expected after approximately three weeks of treatment.[8,11,13]

PREVENTING CMV INFECTION

Strategies for preventing CMV infection in transplant recipients include prophylactic and pre-emptive approaches, as well as a hybrid approach.[1,5,7,11,12]

Prophylactic strategy

The prophylactic strategy involves administering an antiviral drug to all "at-risk" patients for a defined period after transplantation. This duration is typically six months in donor CMV-positive, recipient CMV-negative (D+R) transplants and three months following the use of anti-lymphocyte depleting agents. Prophylaxis has been linked to lower rates of allograft loss and can also prevent the

reactivation of Epstein-Barr virus. However, it's important to note that late-onset CMV infection commonly occurs in D+R- patients after prophylaxis is discontinued.[1,2,5,7,9,11]

Pre-emptive strategy

The pre-emptive strategy involves administering an antiviral drug only to asymptomatic patients who show evidence of early CMV replication, aiming to prevent the development of CMV disease. This approach is not recommended for D+R-patients. It typically involves weekly CMV PCR testing for 12 weeks after transplantation, and if a positive CMV threshold is reached, antiviral therapy is initiated. A benefit of the pre-emptive strategy is a reduced exposure to drug adverse effects.[8-10]

Hybrid approach

A hybrid approach combines elements of both strategies, where short-term antiviral prophylaxis is followed by pre-emptive therapy during the period of CMV disease risk.[11,13,15]

CONCLUSION

In conclusion, this review article highlights the detailed evaluation and the importance of different approaches and emerging modalities for managing post-renal transplant CMV disease in children. However, further randomized, double-blind, controlled trial studies with more adequate sample sizes, as well as meta-analyses, are needed, particularly concerning the paediatric population.

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