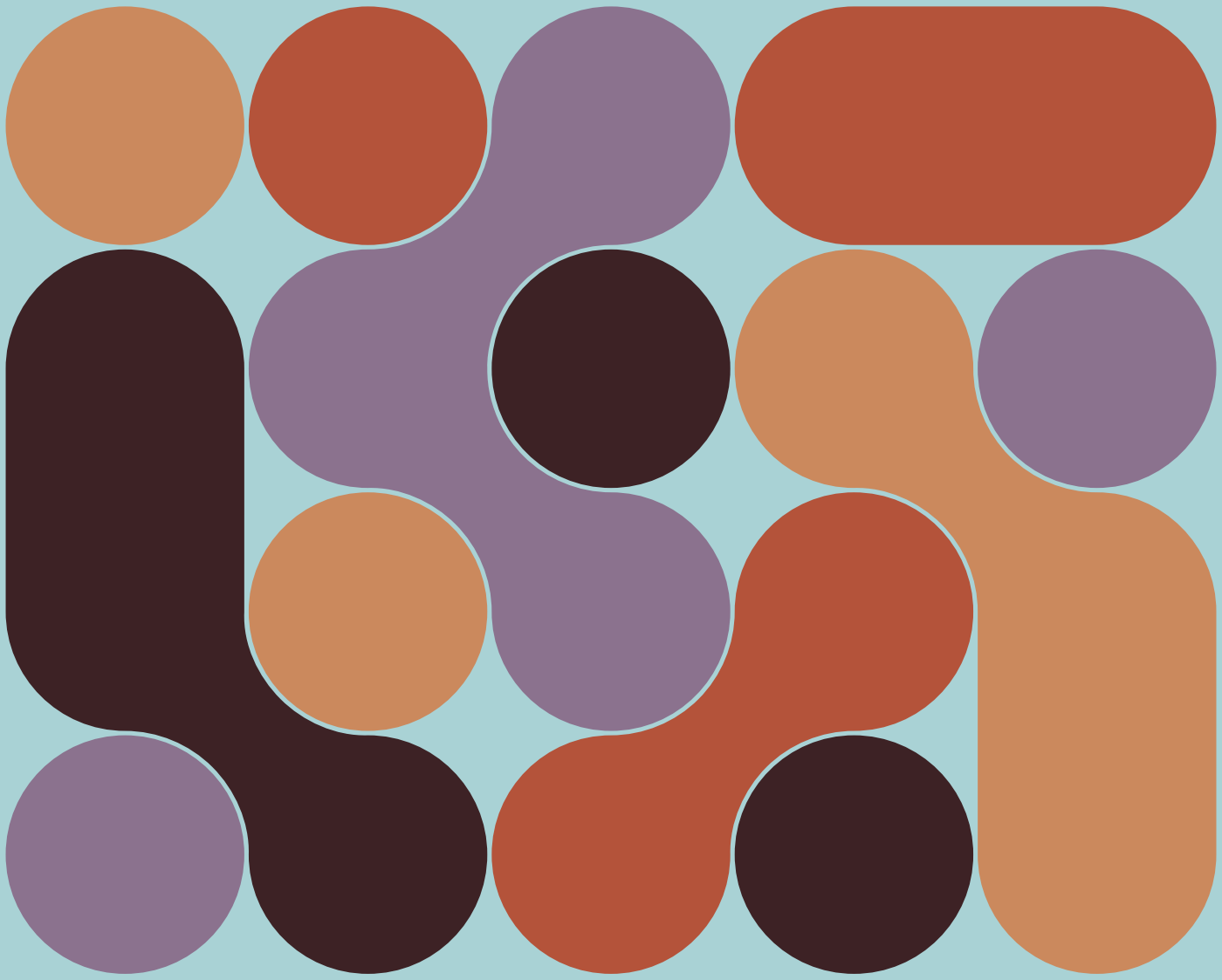
Dialogues in Cytomegalovirus



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Management of Cytomegalovirus in Post-Stem Cell Transplantation

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Introduction

Cytomegalovirus (CMV) is a double-stranded DNA virus from the herpes virus family and is one most important causes of viral infection after allogeneic stem cell transplantation.[1]

In early infancy, this virus can cause a primary clinical or subclinical infection and subsequently remain in a latent state in several types of leucocytes (lymphocytes, monocytes, dendritic cells) and CD34 + cells, under the control of T-cell immune effector cells.[2]

Immunosuppression associated with hematopoietic cell transplantation (HCT), marked by severe and prolonged lymphocytopenia and T-cell function inhibition or dysfunction, may cause CMV reactivation, systemic viral infection and, ultimately, end-organ diseases such as pneumonitis, colitis and retinitis.[3]

The incidence of cytomegalovirus disease is 2-3% in the placebo control groups of several randomized prophylaxis trials, and 5-10% in real-world practice.[4,5]

Risk Factors and Donor Selection

The primary risk factors for CMV disease are the recipient's CMV positive serology; in vivo or ex vivo T-cell depletion; the use of high-dose steroids; the use of an HLA mismatched or an unrelated donor; the occurrence of graft-versus-host disease (GvHD), and cord blood as stem cell source.[6]

Despite significant advances in early diagnosis and management of CMV, a survival disadvantage persists for CMV seropositive patients (R+) compared with D-/R- patients.[7] The impact of using a CMV-negative donor to a CMV-positive patient carries the worst outcome. Data from the European Society of Blood and Marrow Transplantation (EBMT) demonstrated decreased survival rates in the unrelated donor setting when using a myeloablative-conditioning regimen.[8] Additional studies reported delayed CMV-specific immune reconstitution, a higher probability of late CMV reactivation with higher viral load, and CMV disease.[9,10,11]

When possible, a cytomegalovirus-seronegative donor should be selected for a cytomegalovirus-seronegative recipient. A cytomegalovirus-seropositive donor should be preferentially selected for a cytomegalovirus-seropositive recipient.

A seropositive or seronegative donor is suitable for a seropositive recipient undergoing haploidentical hematopoietic stem cell transplantation (HSCT) with post-transplant cyclophosphamide.[12]

Current Strategies for CMV Management Post-SCT

1. Prophylaxis

The prophylaxis approach is utilized for the prevention of CMV infection or reactivation in a high-risk subpopulation.

A meta-analysis comparing six antiviral drugs used for CMV prophylaxis in HSCT demonstrated that the most effective agents for reducing CMV reactivation and disease were ganciclovir and letermovir.[13]

Letermovir is an antiviral drug that inhibits the CMV-terminase complex. It was studied in a phase 3, double-blind trial, in randomly assigned CMV-seropositive transplant recipients, ≥18 years old. Subjects received letermovir or placebo beginning a median of 9 days

post-transplantation, administered orally or intravenously, through week 14 post-transplantation. Dosing was 480 mg per day (or 240 mg per day in patients receiving cyclosporine). Letermovir prophylaxis resulted in a significantly lower risk of clinically significant CMV infection vs placebo by week 24 post-transplantation and improved 24-week overall survival (OS). The safety analysis of the study population demonstrated no significant difference vs placebo in the incidence of adverse effects; time to engraftment; incidence and severity of GvHD; and myelotoxicity.[14] Following this trial, letermovir prophylaxis received the highest score of recommendation by the European Conference on Infections in Leukaemia, 7th edition (ECIL-7).[12]

Retrospective data from real-world use and cost-effectiveness model analysis have confirmed that anti-CMV primary prophylaxis with letermovir reduces CMV infections; results in shorter duration of hospitalization; reduces costs; and improves hematological and renal parameters.[15,16]

In randomized clinical trials on allogeneic bone marrow transplantation, high doses of aciclovir or valaciclovir reduced the risk of CMV infection, but not the risk of CMV disease.[17,18]

Intravenous ganciclovir prophylaxis has additionally been tested in randomized clinical trials for allogeneic marrow transplants and reduced the risk of CMV disease vs placebo; however, they did not demonstrate improved survival rates. No difference was observed in CMV disease risk or patient survival between ganciclovir and valacyclovir prophylaxis regimens, nor between ganciclovir prophylaxis and pre-emptive therapy.[19] Foscarnet prophylaxis has been used solely in uncontrolled clinical trials, and its prolonged use is limited by reported toxicity.[20]

2. Pre-emptive

The pre-emptive approach requires serial blood screening for CMV viremia or antigenemia by PCR-CMV-DNA or pp65 protein detection to initiate antiviral treatment upon detecting significant viremia or antigenemia to prevent CMV disease.[21]

The use of pre-emptive therapy over the past three decades has represented a significant advancement in reducing the incidence of CMV end-organ disease following HCT. When this strategy is employed, the incidence of CMV disease is approximately 5% and 9% by day + 100 and one year post-HCT, respectively.[22]

Whole blood and plasma specimens are equally suitable for CMV DNAemia monitoring. Overall, CMV DNA loads are higher in whole blood, although plasma and whole blood levels significantly correlate.[23]

Quantitative polymerase chain reaction (PCR) assays are more sensitive than viral antigen pp65 detection and are the primary choice for monitoring viral load. However, CMV DNA load monitoring should be performed consistently using the same DNA extraction method, qPCR assay and type of specimen.[12]

Monitoring of the DNA load should be performed at least weekly for the first 100 days post-transplant and for an extended period in patients with persistent T-cell immunodeficiency. Unfortunately, no consensus is available on a viral DNA load threshold for the initiation of antiviral therapy, as the threshold for triggering therapy can be adapted according to baseline or post-transplant risk factors.

In a recent EBMT survey, there was large variability in the threshold of CMV-DNAemia used to initiative pre-emptive therapy. However, the preference was for a CMV load >10^3 copies/mL or IU/mL, both for unmanipulated and ex-vivo T-cell depleted hematocrit (HCT).[24]

First-line Pre-emptive Therapy

Either intravenous ganciclovir or foscarnet can be used for first-line pre-emptive therapy. Oral valganciclovir can be used in place of ganciclovir or foscarnet, except in patients with severe gastrointestinal GvHD. A randomized clinical trial has demonstrated that foscarnet is as effective as ganciclovir for pre-emptive treatment. The efficacy and safety profiles of ganciclovir and valganciclovir were similar. The choice of drug depends on time after HSCT, risk of toxic effects and previous antiviral drug exposure.[25,26]

The duration of therapy should be at least two weeks, targeting at least one negative CMV test. Increasing CMV DNA load (or antigenemia) within the first two weeks of antiviral therapy does not necessitate a change of therapy. If CMV is still detected following two weeks of therapy, a maintenance protocol with once-daily antiviral therapy can be considered. Repeated courses of pre-emptive therapy or a prolonged duration of initial pre-emptive therapy might be needed in patients demonstrating slow decreases in viral load.[26]

Subsequent Lines for Pre-emptive Therapy

A patient experiencing a second episode of CMV infection can usually be retreated with the same drug, with consideration given to common side effects.

The alternative approach using ganciclovir (or valganciclovir), or foscarnet, is indicated in patients with refractory CMV infection. Cidofovir can be considered, however, careful monitoring of renal function is required.[27] The combination of ganciclovir

and foscarnet has been studied in HSCT recipients but demonstrated increased side effects and no improvement in efficacy vs ganciclovir alone.[28]

Maribavir, an orally bioavailable benzimidazole riboside, has multimodal anti-CMV activity, inhibiting CMV DNA replication, encapsidation and nuclear egress of viral capsids via inhibition of the UL97 protein kinase and its natural substrates.[29]

In a phase 3, open-label clinical study, patients with R/R CMV were randomized to maribavir 400 mg twice daily or investigator-assigned therapy (IAT) (valganciclovir/ganciclovir, foscarnet or cidofovir) for eight weeks, with 12 weeks of follow-up. The study reported that maribavir was superior to IAT for CMV viremia clearance and symptom control. In addition, maribavir had fewer treatment discontinuations due to treatment emergent adverse events (TEAEs) than IAT.[30]

Although the current attributable mortality of CMV disease is approximately 1% with pre-emptive treatment, this strategy has some suboptimal characteristics, such as organ toxicity (myelotoxicity for ganciclovir/valganciclovir; nephrotoxicity for foscarnet, cidofovir); the requirement of frequent blood sampling for CMV load monitoring, especially in the first three months following HCT; and the fact that it exposes the patient to the negative impact of any significant CMV load viremia on the outcome.[31]

Treatment of CMV Disease

Antiviral therapy with intravenous ganciclovir is recommended for CMV disease. However, foscarnet can be used instead of ganciclovir if ganciclovir cannot be administered due to toxic effects or antiviral resistance. Valganciclovir can be used instead of intravenous ganciclovir or foscarnet (except in patients with severe gastrointestinal GvHD). The addition of a granulocyte colony-stimulating factor can be considered in the case of neutropenia with prolonged anti-CMV therapy.[12]

Adding high-dose intravenous immunoglobulin to antiviral therapy can be considered for treating CMV pneumonia.[32] However, its use remains controversial as retrospective analysis did not find a positive effect of regular or CMV-specific immunoglobulin on the outcome.[33] Additionally, no data exists indicating any advantage of CMV-specific immunoglobulin over standard immunoglobulin. Adding immunoglobulin to treat manifestations of CMV disease other than pneumonia is not recommended.[34] Intravitreal injections of ganciclovir or foscarnet, combined with systemic therapy, can be used to treat CMV retinitis.

Either foscarnet, cidofovir, or the combination of intravenous ganciclovir and foscarnet, each given at full dose, can be used as a second-line therapy for CMV disease. However, a Phase 3 trial showed the superiority of maribavir for viremia clearance and symptom control to those therapies with R/R (with or without resistance) CMV with fewer treatment discontinuations due to TEAEs.[30]

Antiviral Resistance

Resistance to antiviral drugs is infrequent in HSCT recipients with a variance rate of 0% and 10% between different patient populations (depending on transplant type, age, regimens used, and risk factors), with the highest frequency found in *ex-vivo* T-cell depleted allogeneic HSCT recipients.[35]

Resistance due to mutations in the viral genome is suspected if CMV antigenemia or DNA load increases by more than 1 $\log_{10}$ or less following at least two weeks of appropriate antiviral therapy or progression of CMV disease.[36]

Ganciclovir resistance mutations are typically found in CMV gene *UL97* or *UL54*. Foscarnet and cidofovir resistance is mediated through mutations in *UL54*. Letermovir resistance is most commonly mediated through mutations in *UL56*. Development of double- and triple-resistant strains is rare but does occur.

In light of the limited therapeutic options, drug resistance is a risk factor for CMV diseases and mortality. Maribavir resistance mutations occur in the *UL97* and *UL27* regions of the CMV genome. Maribavir is a valuable option as it is active *in vitro*; in a Phase III clinical trial against CMV strains resistant to ganciclovir, foscarnet or cidofovir, maribavir demonstrated superior symptom control post-therapy.[30,37]

Adoptive T-cell Therapy

Adoptive T-cell therapy with CMV-specific cytotoxic T lymphocytes (CMV-CTLs) can be considered in post-transplant patients with refractory CMV infection.

Several clinical studies have demonstrated the feasibility and efficacy of ex vivo generated donor-derived or third-party-derived CMV-CTLs.[38-40] However, additional data are needed to define the efficacy of CMV-CTLs and their durability of response, especially in unmanipulated transplants where patients receive immunosuppressive treatment.

Conclusion

The real-world incidence of CMV is thought to be around 5-10%, with numerous risk factors implicated in a post-stem cell transplantation setting. Clinicians

may employ multiple strategies for CMV management, including both a prophylactic and pre-emptive approach. Studies have shown that ganciclovir and letermovir are effective prophylactic agents while either intravenous ganciclovir or foscarnet can be used for first-line pre-emptive therapy. Oral valganciclovir can be used in place of ganciclovir or foscarnet, except in patients with severe gastrointestinal GvHD. Subsequent episodes of CMV infection can usually be retreated with the same drug. Alternatively, maribavir, an orally bioavailable benzimidazole riboside, can be used. Studies have shown that maribavir was superior to valganciclovir/ganciclovir, foscarnet or cidofovir for CMV viremia clearance and symptom control with fewer treatment discontinuations due to treatment emergent adverse events. Treatment of CMV disease with intravenous ganciclovir is recommended for CMV disease. However, foscarnet can be used instead of ganciclovir due to toxic effects or antiviral resistance. Valganciclovir can be used instead of intravenous ganciclovir or foscarnet (except in patients with severe gastrointestinal GvHD). Clinicians may also consider maribavir as a second-line therapy for CMV disease.

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Cytomegalovirus in Solid Organ Transplantation

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Introduction

Cytomegalovirus (CMV) is the most frequent opportunistic pathogen in solid organ transplant (SOT) patients. However, the availability of new antivirals and optimized strategies for prevention have dramatically improved its prognosis.[1] CMV, as all herpesviruses, remains in lifelong latency after primary infection. The immune control of CMV replication is driven primarily by CMV-specific T lymphocytes. Previous CMV infection can be diagnosed by the existence of IgG antibodies against CMV, and a negative IgG serology against CMV reflects the absence of CMV-specific T lymphocytes.

CMV can cause a variety of clinical syndromes in SOT patients. The term CMV infection refers to active replication, typically diagnosed by CMV nucleic acid testing in blood, regardless of clinical symptoms.[2] The definition of CMV disease is CMV infection accompanied by clinical symptoms.[2] CMV disease can involve invasion of a variety of organs and can cause fever and cytopenia (CMV viral syndrome). The virus can invade virtually all tissues; the most common sites for tissue invasive CMV disease are gastrointestinal (GI) (gastritis, colitis and hepatitis), retina and lungs.

Risk Factors

The primary predictive risk factor of CMV infection and disease is the donor and recipient CMV serology. As CMV is latent in the organ transplanted it can be transmitted to the recipient. The risk of CMV infection and disease is highest when a recipient with negative CMV serology receives a transplant from a CMV seropositive donor. The lack of CMV-specific T cell responses in a CMV seronegative recipient increases not only the risk of CMV infection, but also the severity of symptoms. The risk of CMV infection and disease is higher when a CMV seropositive SOT recipient receives a transplant from a CMV seropositive donor compared to a CMV seronegative donor. A mismatch in the CMV genotype in latency between the donor and the recipient, and the subsequent transmission of the new CMV explains the increased risk of infection.[3] When both the donor and the recipient are CMV seronegative, the risk of CMV infection is extremely low, although a minority of SOT patients can acquire CMV from community sources.

The second major risk factor for CMV infection is the type of transplant performed. The risk of CMV infection is comparatively higher when the organ contains abundant lymphoid tissue. Lung, small bowel and composite tissue transplantation are associated with a higher risk of CMV infection and disease than liver or kidney transplantation.[4]

In addition, transplant immunosuppression plays a significant role in the risk of CMV complications. Induction therapy with anti-lymphocyte globulins (e.g., thymoglobulin) is associated with higher risk of CMV infection and disease than induction therapy with anti-CD25 monoclonal antibodies (basiliximab).[4,5]

Current Strategies for CMV Disease Prevention in SOT Patients

CMV disease in SOT patients can be prevented by two major strategies: antiviral prophylaxis and pre-emptive treatment. Antiviral prophylaxis consists of the administration of an antiviral capable of inhibiting CMV replication, typically at lower doses than that required for treatment, for a variable period of time. A pre-emptive strategy consists of early treatment of CMV

infection to avoid progression to CMV disease. A pre-emptive strategy requires CMV replication monitoring by periodic nucleic acid testing (NAT) in blood.

Certain differences between antiviral prophylaxis and pre-emptive treatment should be highlighted.[4,6] Prophylaxis inhibits the CMV replication while the patient is receiving the antiviral drug. However, CMV infection following prophylaxis discontinuation is frequent and sometimes is associated with tissue invasive CMV disease. For this reason, the strategy of screening following prophylaxis, which consists of a pre-emptive strategy post-prophylaxis (CMV monitoring by NAT for variable duration and antiviral treatment in case of CMV infection) has been suggested. Antiviral prophylaxis is associated with a comparatively high risk of adverse effects related to the medication. As the majority of patients receive antiviral prophylaxis with valganciclovir, neutropenia leading to severe infections is the most common adverse effect. Naturally, pre-emptive therapy is associated with a higher risk of early CMV infection. In addition, the pre-emptive strategy is more complex than antiviral prophylaxis and typically requires direct supervision by a transplant coordinator.

Antiviral prophylaxis and the pre-emptive approach have demonstrated similar efficacy in CMV disease prevention.[7] In most transplantation centres, antiviral prophylaxis is the preferred strategy for the prevention of CMV disease in SOT patients at highest risk: CMV D+/R-; lung; multivisceral and composite tissue transplants; and following induction therapy with anti-lymphocyte globulins. Typically, pre-emptive therapy is initiated to prevent CMV disease in SOT patients at moderate risk of CMV disease (CMV R+), most likely as the risk of failure complying with this strategy can lead to early life-threatening CMV disease. However, a pre-emptive strategy in CMV D+/R- liver transplant patients is not inferior to prophylaxis and is associated with stronger CMV-specific T cell responses than with prophylaxis.[8]

Antivirals to Prevent CMV Disease in SOT

Currently, valganciclovir is the standard of care for antiviral prophylaxis in SOT patients. In a randomized clinical trial of oral ganciclovir vs valganciclovir, the incidence of CMV disease was not different between arms.[9] However, the rate of neutropenia was higher for valganciclovir (8.2% versus 3.2%) and a subgroup analysis evidenced a higher incidence of end-organ CMV disease among liver recipients who were administered valganciclovir.[9] The recommended dose for valganciclovir prophylaxis is 900 mg daily (adjusted for kidney function). The major side effect related to the use of valganciclovir is neutropenia which occurs in 11% of individuals following four weeks of exposure.[10] Some centres have used valganciclovir 450 mg daily to avoid hematological side effects.[11] However, the low-dose strategy has been associated with a comparatively higher risk of resistant CMV infection and currently it is not recommended.[12]

Foscarnet is not recommended for the prevention of CMV disease due to its intravenous administration, and high risk of nephrotoxicity.[12]

Maribavir was evaluated as pre-emptive treatment of CMV infection in a phase II, randomized clinical trial comparing maribavir (400, 800 and 1200 mg bid) and valganciclovir in recipients of hematopoietic stem cell transplant and SOT.[14] At all tested doses, maribavir demonstrated efficacy similar to that of valganciclovir in eradicating the CMV viremia, with fewer side effects.[14]

Duration of Antiviral Prophylaxis and CMV Monitoring for Pre-emptive Therapy

The duration of antiviral prophylaxis varies depending on the donor/recipient CMV serology and the type of transplant. For CMV D+/R- liver, pancreas and heart transplants, the recommended duration of prophylaxis is 3 months.[4,6] For CMV D+/R- kidney transplant recipients, current guidelines suggest 6 months of prophylaxis due to the fact that a clinical trial demonstrated decreased risk of CMV disease and opportunistic infections with 6 months of prophylaxis compared to 3 months.[15,16] For lung, intestine and composite tissue transplant, current guidelines suggest 6 months of prophylaxis.[4,6] However, a previous clinical study demonstrated a decreased risk of CMV disease in CMV D+/R- lung transplant patients receiving 12 months of prophylaxis;[17,18] many centres have adopted this strategy.

It is recommended that lung, intestinal and composite tissue transplant recipients with positive CMV serology pre-transplant receive 6 months of antiviral prophylaxis, as the risk of CMV disease is very high with these transplants.[4,6] For other CMV seropositive transplant patients receiving induction with anti-lymphocyte globulins, 3 months of antiviral prophylaxis is recommended.[4,6]

Current recommendations for pre-emptive therapy strategy include CMV NAT monitoring from weeks 1 to 12 post-transplant.[4,6] However, for highly immunocompromised patients the duration of monitoring can be extended.[4] The threshold to initiate antiviral therapy depends on the methodology used for CMV NAT testing as there is significant variability in the CMV DNA results reported.[19] Furthermore, the threshold

should be established by each transplant program. Once initiated, the duration of antiviral treatment in a pre-emptive strategy depends on achieving full virological clearance (one negative CMV viral load).[20]

Conclusion

CMV is the most frequent opportunistic pathogen in SOT patients. The main prognostic risk factor for CMV infection is the donor and recipient CMV serology. The risk of CMV infection is highest when a recipient with negative CMV serology receives a transplant from a CMV seropositive donor. Another risk factor for CMV infection is the type of transplant performed, with rates of infection being comparatively higher when the organ contains abundant lymphoid tissue.

CMV disease prevention in SOT patients involves the use of antiviral prophylaxis and pre-emptive treatment. Antiviral prophylaxis and the pre-emptive approach have demonstrated similar efficacy in CMV disease prevention in SOT patients. Valganciclovir is the standard of care for antiviral prophylaxis in SOT patients, however neutropenia has been shown to occur at rates as high as 11% in SOT patients. Maribavir has been studied as pre-emptive treatment compared with valganciclovir and has demonstrated efficacy similar to that of valganciclovir in eradicating the CMV viremia, with fewer side effects. The duration of antiviral prophylaxis varies depending on the donor/recipient CMV serology and the type of transplant performed.

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