

Cytomegalovirus infection in transplant recipients

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Cytomegalovirus infection is a frequent complication after transplantation. This infection occurs due to transmission from the transplanted organ, due to reactivation of latent infection, or after a primary infection in seronegative patients and can be defined as follows: latent infection, active infection, viral syndrome or invasive disease. This condition occurs mainly between 30 and 90 days after transplantation. In hematopoietic stem cell transplantation in particular, infection usually occurs within the first 30 days after transplantation and in the presence of graft-versus-host disease. The major risk factors are when the recipient is cytomegalovirus seronegative and the donor is seropositive as well as when lymphocyte-depleting antibodies are used.

There are two methods for the diagnosis of cytomegalovirus infection: the pp65 antigenemia assay and polymerase chain reaction. Serology has no value for the diagnosis of active disease, whereas histology of the affected tissue and *bronchoalveolar lavage analysis* are useful in the diagnosis of invasive disease.

Cytomegalovirus disease can be prevented by prophylaxis (the administration of antiviral drugs to all or to a subgroup of patients who are at higher risk of viral replication) or by preemptive therapy (the early diagnosis of viral replication before development of the disease and prescription of antiviral treatment to prevent the appearance of clinical disease). The drug used is intravenous or oral ganciclovir; oral valganciclovir; or, less frequently, valacyclovir. Prophylaxis should continue for 90 to 180 days. Treatment is always indicated in cytomegalovirus disease, and the gold-standard drug is intravenous ganciclovir. Treatment should be given for 2 to 3 weeks and should be continued for an additional 7 days after the first negative result for viremia.

KEYWORDS: Cytomegalovirus; Organ Transplantation; Hematopoietic Stem Cell Transplantation.

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INTRODUCTION

Cytomegalovirus (CMV) is a ubiquitous herpes virus that infects up to 60-100% of people in adulthood, and it is one of the main agents involved in infectious complications after transplantation. CMV, similarly to other herpes viruses, establishes a latent infection after initial infection. In the immunocompetent host, the initial infection is generally asymptomatic but may present as an unspecified febrile, flu-like or mononucleosis-like syndrome. In rare cases, the infection presents as a systemic syndrome, affecting many

organs. Additionally, immunocompetent adults may present a clinical syndrome later in life due to reactivation of latent virus or due to new infection by another viral strain. The disease caused by post-transplant CMV (PT-CMV) occurs due to transmission from the transplanted organ, due to reactivation of latent infection, or after a primary infection in seronegative transplant patients (1-5).

CMV infection and disease can be defined as follows (6):

- latent infection – after the initial immune response, the virus persists in a latent state, mainly in myeloid lineage cells, and employs various mechanisms to evade the immune system and to survive.
- active infection – the presence of viral replication, diagnosed by growing the virus in vitro; by the discovery of intracytoplasmic and intranuclear inclusions, which are characteristics of the virus; by viral identification via tissue staining of biopsy material; or by the discovery of evidence of viral replication detected by antigenemia assay or molecular methods.

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- disease – evidence of an infection with symptoms attributed to it.
 - viral syndrome –the presence of signs and symptoms of disease and the confirmation of viral replication in the peripheral blood (detected by antigenemia assay or molecular techniques).
 - invasive disease – the presence of specific symptoms in a target organ and histological findings demonstrating the cytopathic effect of the virus in tissue. In these instances, there may or may not be evidence of viral replication in the peripheral blood.

The most common clinical picture in the transplanted host is a viral syndrome, characterized by fever and malaise as well as leukopenia, thrombocytopenia and elevated liver enzymes. These signs appear from the 3rd to 4th week, with a peak from the 6th to 16th week, and become rare after the 6th month. Upper digestive tract symptoms, and mainly pain, are common. Diarrhea, occasionally containing blood, is more uncommon and is suggestive of colonic involvement. Respiratory symptoms indicate more severe disease and may require admission to an intensive care unit. Additionally, clinical hepatitis, meningoencephalitis, pancreatitis and myocarditis are rare. In contrast to what is found in HIV-infected patients, chorioretinitis is very rare in transplanted patients.

The occurrence of disease caused by CMV in transplanted patients without prophylaxis varies according to the type of transplantation, the serological match between donor and recipient, the immunosuppressive drugs used (patients on mTOR inhibitors have a very low incidence of CMV) and the interference of additional illness risk factors. The incidence is higher in patients undergoing lung or heart-lung transplantation (an incidence of 50-75%) and in patients undergoing pancreas or kidney-pancreas transplantation (an incidence of approximately 50%). The incidence of CMV is between 9 and 23% after heart transplantation, between 22 and 29% after liver transplantation and between 8 and 32% after kidney transplantation (7). Moreover, 30% of patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT) and approximately 5% of patients undergoing autologous HSCT develop CMV disease.

In solid organ transplantation (SOT), the greatest risk factor for CMV disease is a serological mismatch between the donor and the recipient (the recipient is CMV seronegative and the donor is seropositive), (CMV D+ /R-). Furthermore, CMV D + /R+ transplantation and CMV D-/R+ transplantation are considered to be of intermediate risk for the development of disease, and CMV D-/R- transplantation is considered low risk (< 5%) (8,9).

Additional risk factors include intense immunosuppression (as determined based on the transplant center-recommended immunosuppressant protocol and the drugs and doses used), the use of lymphocyte-depleting antibodies (such as antithymocyte globulin, or ATG), acute rejection, advanced age in the donor and/or recipient, HLA mismatch, other concurrent infections (such as with herpes virus 6 or 7) and genetic polymorphisms (9–11). In HSCT, the risk of disease is also higher both in seropositive recipients, regardless of the donor's serological status, and in the presence of graft-versus-host disease (GVHD) (12).

In SOT, the disease caused by CMV occurs mainly between 30 and 90 days after transplantation and is rare after 180 days. Onset may be delayed when antiviral prophylaxis

is used. However, the disease may occasionally develop at other times (13–15).

The deleterious effects of CMV in transplant recipients result from the direct cytopathic effect of the virus on various organs and systems, mainly causing pneumonia, gastrointestinal tract disease, hepatitis, encephalitis, and retinitis.

CMV disease has a major impact on morbidity and mortality in transplant patients. Moreover, the disease contributes greatly to increased use of diagnostic and therapeutic resources and to the overall cost of transplantation. CMV infection may also have indirect effects that influence graft dysfunction, accelerate coronary artery atherosclerosis and increase the risk of other opportunistic infections (16–18).

A proposed definition of the different clinical syndromes is presented in Table 1 (19–22).

■ DIAGNOSIS

Diagnosis of the infection caused by CMV has evolved considerably in recent years. There are two methods used to diagnose active CMV infection: the pp65 antigenemia assay and polymerase chain reaction (PCR), which can be used for the early detection of CMV viral replication. However, there is a tendency to replace the antigenemia assay with molecular methods, particularly in monitoring CMV viral replication after transplantation (23–27).

Traditional diagnostic methods such as culture on human fibroblasts have no practical use because they can take up to two weeks to show a positive result, and even then, they are not indicative of an active infection. Meanwhile, tests using the interferon-gamma release assay (IGRA), such as *Quantiferon* and *ELISpot*, do not yet have a defined role in diagnosis and monitoring.

Serological diagnosis

Serology is useful in determining the serological status of the donor and recipient prior to transplantation to thereby define the post-transplant risk, given that CMV-negative recipients receiving an organ from CMV-positive donors develop more frequent and more aggressive disease. After transplantation, however, the value of serology is limited, and serology has no value for the diagnosis of active disease or infection (28).

Serological diagnosis of CMV infection can be accomplished by dosing the IgM and IgG antibodies. The first antibody to appear is IgM, which may be present in the patient's serum for a long period of time after the infection. Moreover, this antibody may reappear after reinfection, including infection by different strains of the virus, demonstrating that IgM positivity is not diagnostic of a primary or recent infection with CMV. The IgG antibody appears in the blood after 6 to 8 weeks of infection and can persist indefinitely, although with fluctuation in its levels. For this reason, this antibody is used to define the serological relationship between the donor and the recipient (D/R). If the donor's serology is doubtful or inconclusive, it should be considered positive. If the serology is negative in the initial pre-transplant evaluation and there is a long delay until the transplant, the serology should be repeated, especially if the patient received a blood transfusion in the meantime. It is important to remember that the presence of IgG antibody does not protect the individual from reactivation of a latent

**Table 1** - Definitions: CMV syndrome and disease affecting different organs (19–22).

Disease	Presumed diagnosis	Confirmation
CMV syndrome	The presence of one or more of these signs: fever > 2 days, malaise, leukopenia, > 5% atypical lymphocytes, thrombocytopenia, and increased aminotransferases (> 2-fold, except in liver transplantation) plus evidence of active CMV infection	Clinical and laboratory evidence of CMV infection without confirmation of other etiology
Pneumonia	The presence of signs and symptoms of pneumonia (fever, cough, dyspnea, hypoxemia, X-ray changes) plus evidence of CMV infection in the blood and/or bronchoalveolar lavage	Lung disease manifestations plus the presence of CMV in lung tissue based on immunohistochemistry with or without evidence of active CMV infection in the blood or bronchoalveolar lavage
Gastrointestinal disease (esophagitis, gastritis, enterocolitis, colitis)	The presence of signs and symptoms of gastrointestinal compromise plus endoscopic signs of mucosal lesions and evidence of active CMV infection in the blood	Gastrointestinal manifestations plus the detection of CMV in gastrointestinal tissues by immunohistochemistry
Hepatitis	An increase in liver enzymes and bilirubin levels (> 2-fold) in the absence of other known causes plus evidence of CMV in the blood	The presence of increased liver enzymes and bilirubin levels plus the presence of CMV in liver tissue, as determined by immunohistochemistry; note that the presence of hepatitis and CMV in the blood, without histological confirmation of CMV in liver tissue, does not allow for the diagnosis of hepatic invasive disease
Central nervous system disease	Neurological signs and symptoms in the absence of other known causes plus evidence of CMV (as detected by RT-PCR) in the cerebrospinal fluid	Neurological signs and symptoms plus evidence of CMV in brain tissue, as detected by immunohistochemistry
Retinitis	Not applicable	Typical CMV lesions on the retina, as confirmed by an ophthalmologist
Invasive disease in other organs (e.g., nephritis, myocarditis, pancreatitis)	The presence of organ dysfunction in the absence of other known causes plus evidence of CMV in the blood	The presence of organ dysfunction plus the presence of CMV in the target organ tissue, as detected by immunohistochemistry

Evidence of active CMV in the blood: positivity of antigenemia or RT-PCR testing.

viral infection or from a new infection with a different strain of the virus.

Serology in immunocompromised patients can be difficult to interpret due to the patients' impaired humoral responses. Moreover, they can present circulating IgG from transfusions or from treatments with immunoglobulin.

Antigenemia assay

The CMV antigenemia test is a rapid method for the detection of CMV phagocytized by neutrophils in the peripheral blood. In particular, monoclonal antibodies to CMV pp65 protein are used as an early and specific marker of active infection. The blood sample should be collected with anticoagulant, and the results are expressed as the number of polymorphonuclear cells infected in relation to the total number of polymorphonuclear cells counted. The antigenemia assay is comparable to quantitative PCR in that it is a highly specific method for CMV detection and has predictive value for the disease severity, which is related to the number of cells detected. However, serious infections may exist with a low number of positive cells or even in their absence. In general, the number of positive cells has been used as an indicator of when to start preemptive treatment. Although positive cells represent viral replication, a cut-off number of cells specific to each transplant center should be established for disease diagnosis. From one to ten or more cells are accepted as a cut-off number for SOT, and one or two cells are accepted for HSCT. The antigenemia assay is also used to evaluate the response to antiviral treatment, and its disappearance from the bloodstream is considered as a marker of therapeutic efficacy (29,30).

The advantages of the antigenemia assay are that it can be performed soon after blood collection and has a short processing time (approximately 6 hours), enabling early

diagnosis of the infection, and that it does not require sophisticated and expensive equipment and can be performed in medium-capacity laboratories. The disadvantages include the following: the test needs to be conducted immediately after the collection of blood samples (no more than 6 hours later); its quantification is subjective and dependent on the expertise of the person who performs the test; it is not a uniformly standardized method, with extensive variability in its practice, which can compromise reproduction of the method in different laboratories; and it can only be applied if there is an adequate number of circulating cells, which limits its use in patients with leukopenia (the neutrophil count must be greater than 200/mm³), particularly in HSCT recipients. The result may specifically be doubtful in patients with a neutrophil count below 1,000/mm³.

Quantitative PCR

Viral load quantification in CMV by quantitative PCR is the main alternative option for the diagnosis of viral replication and for decision making regarding preemptive treatment and monitoring the response to treatment (28,31). This test is carried out using the real-time PCR (RT-PCR) technique, which provides better accuracy, a faster response time, higher efficiency and a lower risk of contamination compared with conventional PCR. Quantification of the viral load can be conducted using plasma, whole blood or cerebrospinal fluid. In addition to the test's high sensitivity, limited concordance has been observed between *bronchoalveolar lavage* positivity by PCR and systemic infection (32). CMV DNA is generally detected earlier and in greater amounts in whole blood compared with plasma. However, there is a poor correlation of the quantitative values for the viral load test between laboratories, partly due to the



lack of an international reference standard and partly due to variations in the assay. This variation prevents the creation of widely applicable cut-off points for clinical decision making, especially for preemptive treatment strategies (31,33).

Studies have shown that higher viral load values correlate with an increased risk of developing the disease (34). Certain publications reported the same efficacy for preemptive treatment and universal prophylaxis in randomized clinical trials performed with kidney transplant recipients using an intervention cut-off point of $>2,000$ copies/mL of whole blood (35,36). The evolution of the viral load over time might be more important for predicting disease development than any of the absolute viral load values are. The detection limit varies among different viral load tests, and a lower detection limit of more than 1,000 copies/mL (using whole blood or plasma) may be insufficient to detect the disease because certain severely ill patients may present very low viral loads. However, a very sensitive test (detection limit <10 copies/mL) can detect the latent virus, especially if whole blood is used, which limits the clinical usefulness of an extremely sensitive test (28). The results of this test should be available between 24 and 48 hours and should be reported as the number of copies or transformed into logarithms or I.U.

Comparison between RT-PCR and antigenemia assay

Both the antigenemia and the viral load tests for CMV DNA have clinical utility, and in general, there is good correlation, although not uniform, between the CMV antigen levels and viral load values. However, the antigenemia assay has low sensitivity in the detection of CMV reactivation in patients undergoing HSCT who develop viremia before bone marrow grafting and in transplant patients who develop localized disease, such as CMV disease of the gastrointestinal tract. In this case, RT-PCR is more useful (28,37).

Quantitative PCR seems to be superior, more sensitive and faster than the antigenemia assay for the diagnosis of CMV infection and for the detection of CMV reactivation in transplant patients (38–43). A discrepancy between the results of antigenemia and quantitative PCR testing generally occurs when viremia is low, with an average of 0.5 positive cells per field in the antigenemia assay or less than 1,000 DNA copies/mL of plasma in quantitative PCR (39). The decision regarding which test to use depends on many factors, such as the available resources and technical expertise, the patient population, the time requirement, the sample volume and the cost.

Viral resistance

A controversial issue in the management of CMV is the development of viral resistance to the drug used to treat patients. Additionally, few studies have evaluated the development of antiviral resistance in transplant patients (44–46). Sequencing that detects the mutations that cause resistance is considered as the gold standard. For example, ganciclovir-resistant CMV is usually associated with mutations in UL97 (a protein kinase) and UL54 (a DNA polymerase) (47–50).

Histological diagnosis

The analysis of a biopsy of the affected tissue is useful in the diagnosis of invasive disease, both based on the

presence of intracellular viral inclusion and based on the detection of CMV antigens by immunohistochemistry or DNA hybridization, together with an inflammatory response. Due to the impossibility of histological analysis, involvement of the central nervous system can be determined based on the presence of CMV in the cerebrospinal fluid, as detected by RT-PCR.

Prevention and treatment

The prevention of CMV infection aims to reduce the incidence of CMV disease and the indirect effects associated with viral replication (20,28,51). The high-risk groups include D+ /R-, those receiving depleting antibodies (ATG) and lung transplant recipients. In contrast, D-/R- patients have a low risk of developing CMV. Importantly, blood transfusions from CMV+ donors may represent a risk for CMV- patients, who should therefore receive either transfusions from CMV-donors or leukocyte-depleted transfusions.

CMV can be prevented in two ways: by prophylaxis and by preemptive treatment. Both options are effective for preventing CMV disease. There is no consensus on which is the best option, but there is a trend favoring prophylaxis in D+ /R- patients (52).

CMV-specific T cells are crucial for controlling post-transplant CMV replication (53–56). The possible impact of CMV-specific immune response monitoring on the prophylaxis and management of CMV has been considered in HSCT and in SOT and requires validation (57–59).

Transplant recipients receiving mTOR inhibitor treatment have significantly lower rates of CMV disease (60); whether this should alter the prevention strategy requires further study.

No specific vaccine against CMV is available for clinical use.

Prophylaxis

Prophylaxis is the administration of antiviral drugs to all patients (universal prophylaxis) or to a subgroup of patients at higher risk of viral replication (specific prophylaxis) for a predetermined period of time in cases with an increased occurrence of viral replication after transplantation. This approach should be initiated as early as possible. A delayed onset of infection may occur after the discontinuation of prophylaxis, and there is evidence of a lower CMV incidence after prophylaxis suspension following a longer period of drug use (61). Although no consensus has been reached regarding the period of antiviral use, prophylaxis is usually conducted for 3 to 6 months post-transplantation. There is also a tendency to recommend monitoring of the intensity of CMV viral replication after the end of the prophylaxis period during the first year post-transplant. The antivirals used are ganciclovir (intravenous and/or oral) and valganciclovir. Alternatively, oral valacyclovir may be used.

As a rule, prophylaxis is indicated in the following cases: transplantation in CMV D+ /R- and transplantation with the use of induction or with treatment of rejection with ATG. Antiviral drug treatment should begin immediately after transplantation or after the use of ATG. The medication duration is usually three months, although several authors advocate a longer prophylaxis period (28,31,61).

The arguments in favor of prophylaxis are that the use of antivirals would prevent both viral replication and disease and would therefore reduce the indirect effects of viral



replication. Moreover, with this approach, laboratory monitoring of viral replication would not be necessary.

The arguments against prophylaxis are the cost and side effects of antiviral drugs; the probability of occurrence of the disease once the prophylaxis ends; and its association with greater delays in clinical suspicion, diagnosis and treatment, leading to the possibility of greater morbidity and mortality. In addition, those who might require treatment as well as those who might not are medicated indiscriminately.

Another aspect to consider is the increasing incidence of viral resistance in patients undergoing SOT who receive antiviral prophylaxis. The gene related to ganciclovir resistance can be sequenced (UL97) and detected within 24 to 48 hours in certain research laboratories, and the same is expected for the gene UL54, encoding a polymerase, which contains mutations conferring resistance to foscarnet and cidofovir (62,63).

Another possible argument against prophylaxis is the lack of immune stimulation due to the absence of early viral replication, leading to the absence of a specific immune response to CMV (64).

Preemptive treatment

The goal of preemptive treatment is the early diagnosis of viral replication, before the development of the disease. This diagnosis is performed through regular laboratory monitoring for the detection of viral replication. When viral replication is above a predetermined limit, antiviral treatment is indicated to prevent the appearance of clinical disease (hence the term “preemptive,” also called “pre-symptomatic”). There is no default value for the indication of preemptive treatment, so each transplant center must establish this limit. However, from a theoretical point of view, any level of viral replication should be an indication for preemptive treatment to stop the indirect effects of CMV. The main limitation of this approach is the only partial prevention of the indirect effects of viral replication, including effects on graft and patient survival (65–67).

The advantages of preemptive treatment include a lower cost and no incidence of drug side effects because an antiviral drug is not used and the theoretical possibility of stimulating the development and maintenance of a CMV-specific immune response due to viral replication in the absence of antiviral drugs. Furthermore, preemptive treatment avoids the use of drugs in a patient who effectively does not need them. However, by allowing viral replication, indirect effects may be triggered. The disadvantages include the following: blood collection logistics; test costs; the need for laboratory support to obtain the results of viral replication monitoring within the time frame required for immediate initiation of preemptive treatment, when indicated; and the risk of recurrent episodes of replication, with indications for more than one preemptive treatment, especially in patients with increased immunosuppression, lung transplantation or D+ /R- CMV status. Blood samples should be collected frequently (ideally weekly) for a long period of time (3 to 6 months). However, this approach limits patient adherence and may cause preemptive treatment failure.

Comparison between prophylaxis and preemptive treatment

There is no consensus on the best method. Preemptive therapy depends on the logistic routine of CMV monitoring,

the availability of accurate assays, efficient access to results, and rapid initiation of therapy after positive replications. To induce a very rapid increase in viral load in high-risk cases, such as patients with D+ /R- status, lung transplant patients, and those on potent immunosuppression, prophylaxis is probably safer and is more highly recommended than preemptive therapy (31,51).

There have been few comparative randomized studies. Khoury et al. (35) found similar data for the prevention of CMV disease in relation to preemptive prophylaxis compared with treatment, 5 out of 98 patients (5%) developed disease: 4 (8%) in the prophylactic group and 1 (2%) in the preemptive group. As expected, there was a higher rate of viremia with preemptive therapy (59% vs. 29%). Late emergence of viremia (>100 days after transplantation) occurred in 24% of patients undergoing prophylaxis, compared with 0% of the patients undergoing preemptive treatment. In another study, Kliem et al. (66) found a significant reduction in CMV disease in 12 months (17% in the prophylaxis group vs. 50% in the preemptive treatment group). Patients on prophylaxis developed invasive infections later (135 vs. 39 post-transplant days). There was no significant difference in renal function in the short term. However, the incidence of graft loss in the 4th year post-transplant was higher in patients on preemptive treatment (78% vs. 92%). Witzke et al. (68) found respective viremia rates of 38.7% vs. 11% and invasive CMV disease rates of 19.2% vs. 4.4% in the preemptive and prophylaxis groups. Spinner et al. (69) found no long-term (4 years) difference in relation to acute rejection, kidney loss or death in patients on prophylaxis or under preemptive treatment. Reischig et al. (36) found a similar frequency of CMV disease with preemptive treatment and prophylaxis (6% vs. 9%), and the emergence of viremia occurred at 37 vs. 187 days post-transplant. Acute rejection was more frequent in the preemptive group (36% vs. 15%). In two studies, the comparative cost was assessed and was similar in the two schemes, considering the cost of the antiviral drugs and of monitoring by PCR (35,58). Notably, the costs of antigenemia testing are lower than those of RT-PCR.

There is also a hybrid strategy used by certain transplant centers in D+ /R- cases: prophylaxis followed by preemptive treatment to prevent the emergence of late invasive disease (28).

■ ANTIVIRALS

The use of antivirals should be based on standardized doses with respective correction algorithms for the level of renal function (Tables 2 and 3).

Prophylaxis

According to current guidelines (28,70), the prophylaxis options include intravenous ganciclovir, oral valganciclovir, and high doses of oral valacyclovir in renal transplant recipients. Oral ganciclovir has been used, although several studies have showed less optimal outcomes.

Although valganciclovir is the best drug for prophylaxis because it is effective and available in oral form, its high cost limits its use, and it is frequently not available. Therefore, intravenous ganciclovir may be considered, as it is cheaper and widely available, despite the need for intravenous use. This drug has even been used as a three-times-weekly regimen (71). Valacyclovir, although less effective, is also



Table 2 - Antiviral drug doses recommended for prophylaxis according to the glomerular filtration rate, which is estimated based on creatinine clearance

Drug	Creatinine clearance				
	> 60 mL/min	40–60 mL/min	25–40 mL/min	10–25 mL/min	< 10 mL/min dialysis
Intravenous ganciclovir	5 mg/kg/day	2.5 mg/kg/day	1.25 mg/kg/day	1.5-1.25 mg/kg/day three times per week	1.5-1.25 mg/kg/day after dialysis
Oral valacyclovir*	2 g four times per day	2 g three times per day	1.5 g three times per day	1.5 g twice per day	1.5 g/day
Oral valganciclovir**	900 mg/day***	450 mg/day	450 mg 48/48 h	450 mg 2 times per week	not recommended****

* 1 tablet = 500 mg

** 1 tablet = 450 mg

*** certain authors recommend 450 mg/day²

**** intravenous ganciclovir is recommended

Note: valacyclovir and valganciclovir should be given with meals

available in oral form and may be an alternative to no drug at all (72, 73).

Regarding the prevention of CMV disease, treatment with oral CMX001 at a dose of 100 mg twice weekly reduced the incidence of CMV events in HSCT recipients, and diarrhea was a common adverse event at a dose of 200 mg given twice weekly (74).

Treatment

Treatment is always indicated in viral syndrome, in the presence of CMV disease (evidence of CMV infection with signs and symptoms of the disease) and when tissue and organ damage are documented by histological and immunohistochemical changes. During surveillance for preemptive treatment, antiviral drugs should be started as soon as the presence of a replicating virus is detected by either antigenemia or RT-PCR testing.

The gold-standard drug for treatment is intravenous ganciclovir. There is a limited evidence that oral valganciclovir is also effective (75). Therefore, intravenous ganciclovir is the choice for severe infection, but for mild to moderate infection it is possible to use valganciclovir treatment. Acyclovir and valacyclovir are not indicated for treatment. Concomitant use of mycophenolate, azathioprine, mTOR inhibitors or sulfamethoxazole-trimethoprim may favor leukopenia. Modifications of established therapeutic regimens should also be avoided, except in cases of marked leukopenia. In such cases, filgrastim is indicated.

The recommended length of treatment is determined by the weekly monitoring of CMV viral loads; the treatment should be continuous until viral eradication is achieved in one or two assays after a minimum of two weeks. The use of immune-based assays could have potential clinical utility in guiding treatment length and identifying patients with

negative assay results at the end of treatment, who might benefit from secondary prophylaxis (24,28,59).

Risk factors that suggest a need for prolonged treatment include high viremia at the beginning of treatment and CMV recurrence. Risk factors for resistance include prolonged antiviral drug exposure under ongoing active viral replication, high levels of immunosuppressive therapy, and inadequate antiviral doses (28). Drug resistance should be suspected with the persistence of or an increase in viral load in the presence of CMV prophylaxis as well as persistent viral replication and/or clinical progression after two to three weeks of treatment (28,73).

Foscarnet is an alternative choice for ganciclovir-resistant CMV, although frequent side effects, and mainly nephrotoxicity, limit its use (44,76).

No consensus has been reached on the use of secondary prophylaxis after completion of treatment of acute infection. However, certain authors recommend this approach for high-risk patients (28).

SPECIAL SITUATIONS

Hematopoietic stem cell transplantation

CMV reactivation may occur in 30% of HSCT patients and in up to 70% of high-risk patients, such as those with positive serology who received a transplant from a negative donor (77). In total, 30% of patients undergoing allogeneic transplantation and approximately 5% of those undergoing autologous transplantation develop CMV disease. In HSCT, reactivation usually occurs within the first 30 days after transplantation and in those who develop GVHD. CMV can be reactivated throughout the entire period of immunosuppressive drug use (78,79). Mortality in patients who develop pneumonia or disseminated disease may reach 90%. CMV reactivation can also present as an engraftment delay.

Table 3 - Antiviral drug doses recommended for treatment according to the glomerular filtration rate, which is estimated based on creatinine clearance

Drug	Creatinine clearance				
	> 60 mL/min	40–60 mL/min	25–40 mL/min	10–25 mL/min	< 10 mL/min dialysis
intravenous ganciclovir	5 mg/kg twice per day	2.5 mg/kg twice per day	2.5 mg/kg/day	1.25 mg/kg/day	1.25 mg/kg after dialysis
oral valganciclovir*	900 mg twice per day	450 mg twice per day	450 mg/day	450 mg every other day	not recommended**

* 1 tablet = 450 mg

** intravenous ganciclovir is recommended

Note: valacyclovir and valganciclovir should be given with meals



Preemptive treatment reduces the incidence of the disease and the mortality of this agent in this patient population. Ljungman et al. (79) showed that the incidence of CMV disease in patients who received preemptive treatment was 1.8% at 100 days after transplantation and 6.3% at one year after transplantation.

CMV-negative patients with CMV-negative donors should receive only leukocyte-depleted blood products or transfusions from CMV-negative donors. Preemptive treatment is indicated both in autologous and in allogeneic transplantation. Treatment is started during conditioning and is given upon the 100th post-transplant day. Two weekly surveys (antigenemia or RT-PCR testing) are also performed. In pediatric patients with autologous transplantation, treatment is started upon engraftment and is given until the 60th post-transplant day, with weekly surveys (antigenemia or RT-PCR testing). With allogeneic transplants, treatment begins on the 10th day after transplantation and continues until the 100th day. Treatment is also given to patients who develop GVHD. A comparison between the viral load test and the antigenemia test for the recommendation of preemptive treatment in HSCT recipients showed that the use of viral load testing significantly reduced the number of patients who required preemptive treatment, with no increase in CMV disease. Comparable data are not available for SOT.

Lung transplantation

The incidence of CMV infection and disease is higher in lung transplantation recipients than in other SOT recipients, with an incidence of 54% to 92% in patients without CMV prophylaxis (80). In addition to direct morbidity and mortality, CMV infection has been associated with episodes of acute cellular rejection as well as with chronic allograft dysfunction, which is the main limiting factor for the long-term success of lung transplantation (81). Although no study has compared prophylaxis and preemptive therapy in lung transplantation, the high frequency of these complications post-transplant makes the use of CMV prophylaxis essential in lung transplant recipients.

In 2005, an advisory committee of CMV experts established the following recommendations for lung transplant centers (82):

All lung transplant recipients must receive CMV prophylaxis, as follows:

1-Prophylaxis should be performed with valganciclovir 900 mg/day (dose adjusted for the glomerular filtration rate) for at least 100 days;

2-Prolonged prophylaxis (over 180 days) may be considered by all centers, considering a reduction in the incidence of infection/disease and the indirect effects of CMV;

3-Prophylaxis should combine antivirals and CMV immunoglobulin, which is effective for the prevention of CMV infection/disease and which must be considered for high-risk groups (D+ /R- patients and patients using ATG);

4-During the first 6 months after transplantation, including the period of prophylaxis, monitoring of CMV viremia must be performed every 2 weeks (by RT-PCR or pp65 antigenemia testing) in accordance with the local protocols, and after 6 months, monitoring should be performed monthly until the end of the first year after the transplant.

AUTHOR CONTRIBUTIONS

All authors participated in reviewing and discussing the subject. Azevedo LS was the main writer. Pierrotti LC and Yasuda MAS reviewed the manuscript.

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