

# Human cytomegalovirus infection: A considerable issue following allogeneic hematopoietic stem cell transplantation (Review)

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**Abstract.** Cytomegalovirus (CMV) is an opportunistic virus, whereby recipients are most susceptible following allogeneic hematopoietic stem cell transplantation (allo-HSCT). With the development of novel immunosuppressive agents and antiviral drugs, accompanied with the widespread application of prophylaxis and preemptive treatment, significant developments have been made in transplant recipients with human (H)CMV infection. However, HCMV remains an important cause of short- and long-term morbidity and mortality in transplant recipients. The present review summarizes the molecular mechanism and risk factors of HCMV reactivation following allo-HSCT, the diagnosis of CMV infection following allo-HSCT, prophylaxis and treatment of HCMV infection, and future perspectives. All relevant literature were retrieved from PubMed and have been reviewed.

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## 1. Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an effective treatment for hematological tumors (1), which has recently been demonstrated to improve therapeutic effects in patients with autoimmune diseases (2). Due to the lengthy procedure of immune reconstruction, particularly after the use of high-intensity chemotherapy to suppress hematopoiesis and the application of T-cell depletion, the occurrence of post-transplant infection has become a prominent complication following allo-HSCT (3). Viral infection is the leading cause of infectious mortality in 30% of patients following transplantation (4). For decades, opportunistic cytomegalovirus (CMV) infection has been the most common complication following allo-HSCT, resulting in mortality (5). Recipients may experience primary human (H)CMV infection, re-infection, re-ignition and co-infection following transplantation (6). CMV immunoglobulin G (IgG) is a marker of HCMV infection, the positive rate of which reaches 50.0-92.2% in healthy adults worldwide, with rates increasing with age (7-10). Following initial HCMV infection, healthy individuals may exhibit no obvious symptoms in their lifetime, and HCMV can also exist in a latent state (11,12). However, infection in immunosuppressed individuals may be more likely to occur due to lack of CMV-specific cytotoxic and helper T cells (13). Active HCMV infection is one of the most common complications following allo-HSCT, which may be fatal for patients receiving transplantation (13). In addition to HCMV-associated diseases that exhibit a high mortality, such as asymptomatic viremia, DNAemia, antigenemia, esophagitis, gastroenteritis, hepatitis, retinitis, pneumonia and encephalitis, HCMV infection is also associated with graft vs. host disease (GVHD), and the increased incidence of other pathogenic infections such as Epstein-Barr virus, varicella-zoster virus and child adenovirus (13).

HCMV is a double-stranded DNA  $\beta$ -herpes virus (235,000 base pairs), also known as herpes virus 5, that contains >200 potential open reading frames (14,15). HCMV synthesizes a series of proteins after entering the host cell,

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*Abbreviations:* allo-HSCT, allogeneic hematopoietic stem cell transplantation; HCMV, human-cytomegalovirus; GVHD, graft vs. host disease; IL, interleukin; TCM, central memory T cells; NPS, non-protective signature; PS, protective signature; SOCS, cytokine signaling genes; LET, letermovir; AML, acute myeloid leukemia

*Key words:* CMV, allo-HSCT, prophylaxis, preemptive treatment, cellular immunotherapy, hematological malignancy

which are divided into immediate early protein (IE), delayed early protein and late protein, according to the time at which they are produced (16). These proteins are synthesized within 2, 24 and after 24 h, respectively (17).

## 2. Mechanism of HCMV reactivation following allo-HSCT

HCMV is latent in the peripheral monocytes and endothelial cells of several organs. Distinct organs, tissues and cell transplants can transmit HCMV. The latency of primary HCMV infection relies on its multiple and complex immune evasion mechanisms to evade the host immune response (18,19). Interferon (IFN)-mediated innate immunity is one of the first lines of the host defense mechanism (12,20). Specific genes encoded by HCMV are associated with the downregulation of IFN-mediated innate immunity (11). In addition, HCMV infection upregulates the function of ligands targeting the natural killer cell activating receptor, natural killer group 2, member D (21). However, the presentation of these ligands on the surface of cells is suppressed by certain HCMV-induced genes, including UL16 and UL142, which encode proteins, and microRNA (miRNA/miR)-UL112, which encodes a miRNA (12,22). Furthermore, HCMV influences the expression of CD155 by upregulating UL141, exposing the receptor on the cell surface to avoid recognition (23). Interleukin (IL)-10 serves as an inhibitor, suppressing the secretion of several cytokines from helper T cells, including IFN- $\gamma$  and IL-2 (24,25). This in turn attenuates the production of inflammatory cytokines from monocytes and macrophages, decreasing the expression of major histocompatibility complex (MHC)-II molecules and subsequent antigen presentation (26). IL-10 also encodes proteins that act as host inflammatory cytokines, resulting in a decrease of local cytokine effectiveness (27). Cheung *et al* (20) suggested that HCMV is associated with the production of IL-10 homologs, which serves an immunosuppressive role during the incubation period of infection. In addition, US2 and US11 have been demonstrated to inhibit the degradation of target MHC-I molecules within the cytoplasm, resulting in destruction by proteasomes. US3 interferes with molecular chaperone related antigen peptide loading by containing MHC-I within the endoplasmic reticulum. Furthermore, US6 suppresses the transporter associated with MHC-I antigen processing. The expression of these genes allow infected cells to escape immune clearance (Fig. 1) (28,29). However, latent infection is established when the virus spreads to and is persistently present in various cells, including myeloid cells (such as monocytes and CD34 cells), endothelial cells, epithelial cells (including retinal cells), smooth muscle cells, fibroblasts, leukocytes and dendritic cells (30,31). Endothelial and hematopoietic cell infection may lead to the spread of the virus within various systems of the host (32). In addition, the infection of ubiquitous cell types, such as fibroblasts and smooth muscle cells, provides a platform for effective virus proliferation (33). CMV-specific CD4 and CD8 T cells appear successively in the peripheral blood. CD4 T cells secrete helper T cell-type cytokines, such as IFN- $\gamma$  and tumor necrosis factor (TNF)- $\alpha$ . CD8 T cells can lyse CMV-peptides to present target cells (34,35). However, during latent infection, these specific T cells fail to eliminate HCMV (12).

Following myeloablative conditioning, recipient immune cells and malignant or defective cells are eliminated, meaning that allo-HSCT recipients must go through a period of pancytopenia for days to weeks depending on the source of stem cells (5). The adaptive immune system is subsequently restored slowly over a period of several months to 1-2 years (36). In the early stages following allo-HSCT, transferred immunity is only maintained for a limited period, after which a gradual decrease is observed (37). In addition to hematological disease itself and the drugs administered during myeloablative conditioning, immunosuppressive agents are used to prevent GVHD, which can further delay immune reconstruction, increasing patient susceptibility to several opportunistic infections (12,38). After allo-HSCT, the immune system is gradually restored following neutrophil engraftment; however, the recovery of lymphocyte function takes an extended period (39). At this point, CMV ends its latent period (3). It has been demonstrated that the activation of multiple pathways can reactivate latent HCMV (40). However, whether a cross-over mechanism exists between each pathway is yet to be elucidated. Anti-lymphocyte antibodies used for induction therapy can induce TNF- $\alpha$  secretion and activate the NK- $\kappa$ B1 pathway, stimulating the transcription of the HCMV IE gene, leading to the resurgence of latent HCMV (41). Simultaneously, antibody treatment can clear T cells, resulting in the lack of T-cell immunity against CMV and decreased immunological surveillance for HCMV (42). In the event of rejection, latent HCMV can be activated through the NK- $\kappa$ B1 pathway (38). Inflammation and stress can activate the expression of IE through the cAMP pathway (43). Ischemia-reperfusion injury activates activator protein-1 (AP-1) through the AP-1 pathway (38). Rejection following transplantation typically occurs prior to HCMV activation (44). Activation of the NK- $\kappa$ B1 pathway results in the transcription of HCMV genes that induce viral infection (45). Subsequent anti-rejection therapy, such as hormonal shock therapy or the application of antithymocyte globulin (ATG) drugs, inhibit or destroy immune function against HCMV (Fig. 2) (44).

T cell-driven cellular immunity is known to control CMV replication, and the lack or delay of CMV-specific CD4- and CD8-T lymphocyte recovery can lead to CMV recurrence and CMV-associated diseases (46-48). CMV reactivation is usually associated with a high frequency of GVHD, which may partially lead to enhanced T-cell reconstitution in patients with HCMV infection (12). A previous study demonstrated that the presence of CMV-specific cytotoxic T lymphocytes (CTL) in CMV seropositive recipients is associated with faster T-cell reconstitution, which may induce donor allogeneic reactivity (49). The successful elimination of residual host hematopoietic function is therefore reflected by the complete donor chimerism (50). In addition, suppression of cytokine signaling genes (SOCS) can also explain the close association between CMV reactivation, GVHD and donor chimerism (51). SOCS is associated with the regulation of T-cell homeostasis and the negative feedback mechanism induced by cytokine signaling, involving IFN- $\gamma$  or interleukins (51). Previous studies on SOCS gene expression have demonstrated that SOCS1 expression is significantly lower in patients with GVHD compared with post-transplant patients without GVHD (37,51,52). Furthermore, SOCS1 expression is

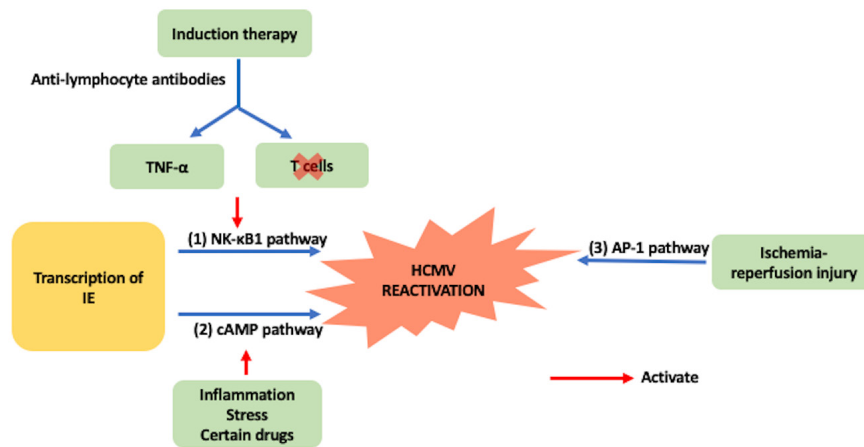


Figure 1. Mechanism of HCMV reactivation. There are three main pathways associated with the reactivation of HCMV. (1) The NK-κB1 pathway: Anti-lymphocyte antibodies used in induction therapy can induce TNF-α secretion and clear T cells, which subsequently activates the NK-κB1 pathway, stimulating the transcription of the HCMV IE gene, leading to the resurgence of latent HCMV. (2) The cAMP pathway: Inflammation, stress activate the expression of IE through this pathway. (3) The AP-1 pathway: Ischemia-reperfusion injury activates AP-1 through this pathway. HCMV, human cytomegalovirus; TNF, tumor necrosis factor; IE, immediate early protein; AP-1, activator protein-1.

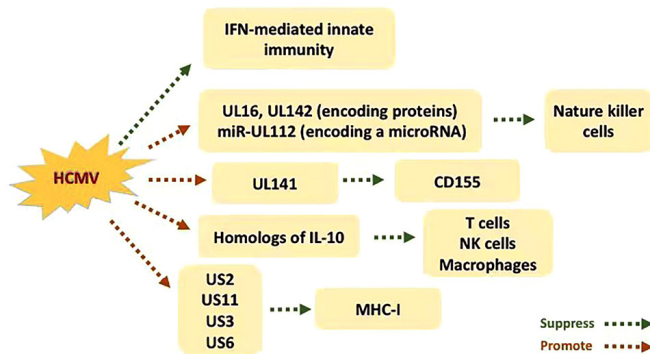


Figure 2. Immune evasion mechanism of HCMV. Due to the gene encoded by HCMV, effects of IFN-mediated innate immunity are downregulated, and HCMV infection suppresses the function of ligands for nature killer cells via UL16, UL142 (encoding proteins) and miR-UL112 (encoding a miRNA). HCMV also influences CD155 expression, which is exposed on the cell surface following infection, by encoding UL141 to avoid recognition. In addition, HCMV is associated with the production of homologs of IL-10, which play an immunosuppressive role during the period of incubation. US2, US11, US3 and US6 expression allow infected cells to escape immune clearance. HCMV, human cytomegalovirus; IFN, interferon; miRNA/miR, microRNA; IL, interleukin; IE, immediate early protein; AP-1, activator protein-1; MHC, major histocompatibility complex.

significantly lower in patients with chronic GVHD than those with acute GVHD (53). In addition, our previous study revealed that SOCS1 expression is significantly higher in patients with CMV reactivation than those with non-CMV reactivation (53). Conversely, SOCS3 expression is decreased in all HSCT recipients (53,54). These data explain the molecular association between HCMV reactivation and allo-HSCT.

### 3. Risk factors of HCMV reactivation following allo-HSCT

**CMV donor (D)/recipient (R) serostatus.** CMV serological status, that is, CMV-IgG (+) and (-), is one of the main risk factors associated with the incidence and mortality of patients with CMV disease following stem cell transplantation (55).

According to previous studies, recipients with a negative CMV serostatus receiving CMV seropositive donor grafts (D+/R-) have the highest risk of mortality following transplantation (56,57). However, other studies have demonstrated that although the risk of infection in patients that are D+/R+ is lower, the survival time of grafts and recipients is shorter than that of D+/R- individuals (58-60). However, the association between CMV serostatus and CMV-positive recipients (R+) remains controversial.

**Graft source.** Currently, the main sources of graft stem cells for transplantation are bone marrow, peripheral blood stem cells and umbilical cord blood (61). Trensche *et al* (62) demonstrated that the incidence of persistent CMV antigenemia and CMV-related interstitial pneumonia following peripheral blood stem cell transplantation significantly decreases compared with bone marrow transplantation, which may be due to the varying immune reconstitution times following different graft transplantations. In addition, Uppuluri *et al* (63) reported that the incidence rate of HCMV reactivation in pediatric patients receiving allo-HSCT from matched-related donors, unrelated peripheral blood stem cells, unrelated umbilical cords and mismatched or haploidentical grafts were 3.0, 33.3, 17.4 and 36.5%, respectively. Furthermore, Boeckh *et al* (64) suggested that patients receiving autologous stem cell transplantation have a lower CMV disease morbidity than patients receiving allogeneic stem cell transplantation.

**Population of CMV-specific T cells.** In healthy individuals, both CD8<sup>+</sup> and CD4<sup>+</sup> T cells, which target certain CMV peptides (65), are significant for the prevention of CMV infection (66). The proportion of the immune response devoted to CMV increases with age in seropositive individuals. The T-cell repertoire and subdominant responses also incorporate other CMV proteins, including glycoprotein-H and pp28 (67). CD8<sup>+</sup> cells recognize the epitopes of CMV proteins in a manner that is determined by human leukocyte antigen (HLA) (67). The major tegument protein, phosphoprotein 65 (pp65), and IE-1 are the most extensively studied



immune targets in HSCT recipients (68,69). According to previous studies, CMV-specific CD8<sup>+</sup> central memory T-cell (TCM) levels in patients before HSCT serves a significant role in long term clinical response (70,71). Liu *et al* (72) revealed that patients with higher populations of CMV-specific CD8<sup>+</sup> TCM exhibit an improved therapeutic response than those with low populations of CMV-specific CD8<sup>+</sup> TCM. In addition, the morbidity of CMV-related diseases is lower in the same patients. LaMattina *et al* (73) demonstrated that CMV-specific T cells are associated with the proliferation of the other T-cell subsets and clonogenesis.

**Immunosuppressive regimen.** Patients are routinely administered thymoglobulin, cyclosporine, alemtuzumab and glucocorticoid shock therapy as treatment following allo-HSCT (74). However, these drugs have been reported to increase the risk of HCMV reactivation (73,75). In addition, the increased use of immunosuppressive agents is an important factor that affects HCMV reactivation (76). Kobashigawa *et al* (77) revealed that the combination of tacrolimus and mycophenolate mofetil achieve a more effective response with less side effects. Furthermore, previous studies have suggested that the application of everolimus and calcineurin inhibitors without steroid treatment can markedly improve the incidence rate of CMV antigenemia (78-80). Collectively, it has been demonstrated that immunosuppression regimens are closely associated with CMV infection.

**GVHD.** GVHD is caused by a series of 'cytokine storms' stimulated by T cells in allogeneic donor grafts following transplantation, which greatly enhances its immune response to recipient antigens (81). Target cells are subsequently used to initiate cytotoxic attacks, of which the skin, liver and intestine are the primary targets (82). Miller *et al* (83) demonstrated that CMV-specific cytotoxic T cells may serve an important role in CMV infection control. The incidence of GVHD and the treatment of immunosuppression limits the proliferation of CMV-specific cytotoxic T cells, thus increasing the chance of CMV infection (84). Nutrient absorption and the physical fitness of patients is weakened, which further increases the risk of CMV infection (85,86). Univariate analysis has revealed that the rate of CMV infection in patients with acute grade 0-I GVHD following transplantation is 51.9%, and the rate of patients with acute grade II-IV GVHD is 92.3% (87). In addition, multivariate analysis has demonstrated that patients with acute grade II-IV GVHD exhibit a higher CMV infection rate following transplantation (87).

**Other risk factors.** Other risk factors for reactivation in allo-HSCT recipients include advanced age, co-infection with human herpes virus 6 or human herpes virus and HLA incompatibility (88).

#### 4. Prediction of CMV infection following allo-HSCT

The prediction of CMV-related diseases is important. Due to primary hematological diseases, certain drugs (such as ATG) and immunosuppressive therapies applied after allo-HSCT or GVHD compromise the immune system of patients (89). In addition, the speed of immune system recovery in different

recipients is another contributing factor (90). Given that the resistance of patients to CMV following allo-HSCT mainly depends on CMV-specific cytotoxic T-cells, CMV-specific cell-mediated immunity serves an important role in reducing the risk of CMV-related diseases (90). Yong *et al* (91) revealed that the quantification of CMV-specific T cells may predict the risk of CMV-related disease. Furthermore, as CMV-specific T cells can be measured by the production of IFN- $\gamma$ , IFN- $\gamma$  ELISpot assays serve an important role in predicting the immunity of CMV-specific T cells (92-94). In addition, Camargo *et al* (41) suggested that determining the phenotype of CMV-specific T cells, the non-protective signature [NPS; IL-2<sup>-</sup> IFN- $\gamma$ <sup>+</sup> TNF- $\alpha$ <sup>+</sup> and macrophage inflammatory protein (MIP-1 $\beta$ )<sup>+</sup>] and the protective signature (PS; IL-2<sup>+</sup> IFN- $\gamma$ <sup>+</sup> TNF- $\alpha$ <sup>+</sup> and MIP-1 $\beta$ )<sup>+</sup>), alone or in combination may be used to determine the risk of CMV infection more efficiently. In addition, patients with high NPS and low PS exhibit an increased risk of CMV infection (41). Low levels of NKG2C copies within the donor and the DNA load of torque teno virus may also be a predictor of CMV infection (95,96). Previous studies have demonstrated that suppression of SOCS, which is associated with IFN- $\gamma$  or interleukin negative feedback, and with measuring the function of T cells (97), can explain the association between CMV reactivation, GVHD and donor chimerism (52-54). SOCS1 is expressed at low levels in patients with GVHD than those without GVHD, and in patients with chronic GVHD than those with acute GVHD (54). SOCS1 expression is also higher in patients with reactivated CMV (53). In a previous study where patients simultaneously exhibited CMV reactivation and GVHD, SOCS1 expression decreased compared with patients only exhibiting CMV reactivation (54). However, SOCS3 expression was downregulated in all patients following transplantation (51).

For patients with a high risk of CMV-related disease, several techniques used for immune monitoring, such as measuring CMV-specific T-cell function, are effective for the improvement of transplantation outcome. However, further studies are required to confirm these results.

#### 5. Diagnosis of CMV infection following allo-HSCT

CMV-mediated disease is diagnosed when patients test positive for CMV serum antigens or produce a positive viral culture following infected tissue analysis, whilst demonstrating corresponding clinical symptoms (98). CMV pp65 antigenemia assays and the amplification of CMV DNA are currently the most used laboratory techniques for the detection of CMV infection (99-101). CMV pp65 antigenemia assays detect CMV pp65 antigens. Furthermore, PCR is performed to detect CMV DNA viral load (102). Bhatia *et al* (99) demonstrated that the sensitivity and specificity of the pp65 antigenemia assay were sufficient to use for the early diagnosis of CMV infection. The pp65 antigen is present in neutrophils and has a semi-quantitative association with CMV virus replication. Since the pp65 antigenemia value usually significantly increases during the first week of CMV treatment, the assay results over this period must be taken seriously (103). This method of detection is simple, easy to implement and requires inexpensive equipment. However, in the absence of standard values, the results may be affected by subjective factors (103). In addition, the

requirements for counting neutrophils are high (104). Despite its low specificity, quantitative DNA-detection techniques have an observable sensitivity and can demonstrate patient prognosis by measuring viral load (99). However, since the results of PCR are affected by the type of specimen used, only plasma or whole blood should be selected for serial viral load testing (105,106). In addition, to differentially diagnose patients with CMV-mediated pneumonia and pulmonary shedding, the quantification of CMV DNA load in bronchoalveolar lavage may be necessary (107,108). Furthermore, the pp67 assay may determine advanced L-mRNA and reflect active HCMV infection, which makes it an effective method for monitoring CMV infection (109).

## 6. HCMV infection prophylaxis

*HCMV prophylaxis.* CMV prophylaxis is mainly aimed at patients with high-risk CMV infection following allo-HSCT (110). Patients with a high risk of CMV include those that are anti-CMV positive following transplantation, those receiving transplants from unrelated donors, those with donor HLA incompatibility and those receiving T lymphatic transplantation (111). Preventive measures include donor selection, blood product handling and the application of antiviral drugs (112).

*Choice of donors and handling blood products.* If both donors and recipients are CMV-IgG negative, recipients are less likely to develop CMV infection following allo-HSCT (13). Thus, for CMV-IgG negative recipients, priority should be given to CMV-IgG negative donors (13). The risk of CMV infection and CMV disease in patients with this combination of donor and recipient serotypes is significantly lower compared with patients demonstrating other serotype combinations (113). The main route of CMV infection is blood transfusion (114). However, Boeckh and Ljungman (13) recommended that if the donor and recipient match at HLA-A, HLA-B or HLA-DR sites, but are seropositive, the matching donor is preferred. In addition, age and blood type should also be taken into consideration when selecting suitable donors (43).

A previous study revealed that blood products obtained after leukocyte depletion effectively decrease the incidence of CMV infection (115). Vamvakas (113) reported that CMV seronegative blood components should be selected over white blood cell reduced blood components to effectively prevent CMV infection. The removal of leukocytes from blood products primarily occurs through filtration, decreasing CMV infection via transfusion. Traditionally, this process is used to screen CMV seronegative blood products and prevent CMV infection (115). However, this screening technique is difficult as it requires increased manpower and material resources (115). In addition, due to the high incidence of CMV infection in certain territories, it may be difficult to obtain CMV seronegative blood products (115).

*Application of immunoglobulins (IVIG).* The role of IVIG in preventing CMV infection is controversial. Previous studies have demonstrated that IVIG serves no preventive function in CMV diseases and may also cause other serious complications, such as interstitial pneumonia (58,116-118).

In addition, Malagola *et al* (119) affirmed the clinical therapeutic effect, safety and tolerance of anti-CMV specific immunoglobulins, such as Megalotect. Furthermore, HCMV immunoglobulin has been approved for use in high-risk lung transplant recipients by the Food and Drug Association of the United States (120). Notably, although decreasing immunosuppression to the greatest extent possible is crucial, caution must be used when considering IVIG.

*Application of antiviral drugs.* The antiviral drugs currently administered to prevent CMV infection include ganciclovir, valganciclovir, foscarnet and cidofovir (Table I). However, the use of antiviral drugs as preventive treatment remains controversial. A recent retrospective study evaluated the effectiveness of antiviral drug administration for the prevention of CMV, the results of which revealed that the regimen was only partially effective (121). An additional prospective study compared the use of valganciclovir with a placebo. The results demonstrated that whilst valganciclovir prophylaxis was effective in decreasing CMV reactivation, it did not decrease CMV infection or mortality, indicating that its effect was not superior when compared with preemptive treatment (122). Thus, due to the disadvantages and adverse drug reactions associated with antiviral drugs, including bone marrow suppression, the majority of HSCT recipients receive preemptive treatment rather than prophylaxis (123).

*Vaccine development.* The development of safe and effective vaccines for CMV has been the focus of recent medical research. As such, there are currently several vaccines under development (124-127). Adjuvant recombinant protein vaccines, which comprise envelope glycoprotein and DNA plasmid, peptide-based vaccines, vectored vaccines and peptide vaccines are currently used against CMV (125). Among those proposed, a specific bivalent DNA vaccine, named ASP0113, is the most studied. However, phase two clinical trials have indicated that whilst the vaccine demonstrates certain antiviral effects, its immunogenicity is not statistically significant (128). Despite these results, phase three clinical trials are currently underway (126). In addition, another vaccine derived from soluble recombinant glycoprotein B (gB) with the adjuvant MF59 and CMV monoclonal is being developed (127). In conclusion, the application of antiviral vaccines requires additional research and development.

## 7. Treatment of HCMV infection

*Preemptive therapy.* Preemptive treatment refers to immediate antiviral administration when CMV antigenemia or viremia first occurs following transplantation. Recently, the application of preemptive treatment has significantly decreased the incidence and mortality of CMV-related diseases following allo-HSCT (129). In addition, the length of treatment required for infection has been shortened, and the incidence of adverse reactions has improved (130). Thus, the success of preemptive treatment primarily depends on the sensitive detection of CMV antigenemia (13). If treatment is performed before detecting the virus, some patients may be treated unnecessarily. Any adverse reactions because of drug administration may therefore increase the probability of infection by other

Table I. Types and properties of standard therapies in prophylaxis and preemptive therapy of CMV infection.

Drug	Properties	Administration route	Side effects	(Refs.)
Ganciclovir	Inhibits virus replication by interfering with the action of viral DNA polymerase	Intravenous	Myelosuppressive effect, fever, rash, diarrhea	(135,140,143)
Foscarnet	Pyrophosphate analog, selective inhibition of pyrophosphate binding sites at CMV DNA polymerase	Intravenous	Renal toxicity, neurotoxic effects, anemia, headache, Nausea; can cause a fixed drug reaction on the penis	(149)
CDV	Nucleotide analog, is converted to the active diphosphoryl form by the host kinases, and CDV disphosphate acts as a competitive inhibitor of the viral CMV DNA polymerase, causing premature chain termination of viral DNA synthesis	Intravenous	Nephrotoxic effects	(145,149)
Valganciclovir	Prodrug of ganciclovir	Oral	Gastrointestinal toxicity, renal toxicity	(135)
Letermovir	Suppresses the CMV-terminase complex	Intravenous or oral	Prone to drug resistance	(150)

CMV, cytomegalovirus; CDV, cidofovir.

bacterial or fungal agents (13). In addition, receiving treatment too late may also affect the antiviral response of patients (131). With use of the CMV pp65 antigen test or PCR, preemptive treatment can be undertaken at a targeted viral load (89). The target viral load varies according to the risk of developing CMV-related diseases and current immunosuppression (132). Drugs currently used for preemptive treatment include ganciclovir, valganciclovir, foscarnet and cidofovir (Table I). Under normal circumstances, preemptive treatment should be maintained until the relevant symptoms are resolved and the CMV serum test is negative (89). If the patients' initial viral load or pp65 antigenemia assay is positive, treatment is maintained until the PCR/pp65 antigenemia assay turns negative. Subsequently, patients should receive maintenance treatment for a varying period (89). The length of maintenance treatment varies from 0-6 weeks depending on factors such as the patients' sensitivity to treatment, drug side effects and the risk of relapse (133).

Most transplant centers worldwide use ganciclovir as the drug of choice for early treatment (134). As an inhibitor of DNA polymerase, ganciclovir inhibits the replication of viral DNA *in vivo* to prevent viral infection (112,135). Winston *et al* (136) revealed that when administering ganciclovir prior to or following allo-HSCT, the incidence rate and severity of CMV infection decreases, despite the suppression of bone marrow function. Similar results have been demonstrated in previous studies (64,137,138). The myelosuppressive effect of ganciclovir may be improved by administering granulocyte-colony stimulating factor (G-CSF) alone or in combination with anti-CMV immunoglobulins (139,140). However, ganciclovir is inefficient in treating interstitial pneumonia following transplantation (141).

As the antiviral immunity of patients differs before and after 100 days of transplantation, the corresponding preemptive treatment regimens also differ (142). According to guidelines (142), preemptive treatment within 100 days after transplantation is suitable for patients who have a high risk of CMV infection following autologous stem cell transplantation, and for patients receiving allogeneic stem cell transplantation who have tested positive for CMV antigenemia or viremia for the first time after transplantation (143). The preferred treatment for these patients is inducive intravenous 5 mg/kg<sup>-1</sup>/d<sup>-1</sup> ganciclovir administered twice a day for 7-14 days, with maintenance therapy once a day until two consecutive tests are negative. In addition, preemptive treatment after 100 days of transplantation is suitable for various patients who achieve two consecutive CMV viremia results or PCR positive tests, including those receiving allogeneic hematopoietic stem cell transplants, GVHD patients receiving steroid therapy or patients receiving CMV antiviral therapy within 100 days of transplantation (131). Due to the myelosuppressive effect of ganciclovir, previous studies have suggested decreasing its dose to a degree that does not change the antiviral effect (89,144). According to a recent study, the dosage should be adjusted based on viral load and that low-dose ganciclovir administered at the beginning of preemptive treatment may be safe and feasible (145). It may also greatly improve the side effects of treatment (89).

Valganciclovir is a prodrug of ganciclovir and demonstrates a good oral bioavailability. A previous study has demonstrated that the blood exposure level of ganciclovir after oral valganciclovir administration is higher than intravenous ganciclovir (146). Oral administration is also more convenient and avoids related infections caused by intravenous administration. In addition,

Table II. New drugs against CMV in clinical trials.

Drug	Year	Clinical phase	Properties	Administration route	Dose	Efficacy	Side effects	(Refs.)
Brincidofovir	2019	Phase 3 trials	Bioavailable lipid conjugate of cidofovir, long half-life, absence of nephrotoxicity	Oral	100 mg (at alternating ¾ day intervals)	Effective in anti-CMV virus	Gastrointestinal toxicity	(145,165)
Maribavir	2019	Phase 2 trials	NA	Oral	400 mg twice daily	Similar to that of valganciclovir for clearing CMV viremia	Gastrointestinal toxicity	(119,167)
CMV, cytomegalovirus; NA, not available.								

due to its myelotoxicity and similar side effects to ganciclovir, close monitoring of patients during treatment is required (147).

Furthermore, a randomized controlled trial revealed that foscarnet demonstrated similar effects to ganciclovir but without granulocytopenia, making it suitable for patients exhibiting bone marrow suppression (148). The main adverse reaction following foscarnet administration is electrolyte disturbance; however, this can be easily corrected by intravenous fluid replacement (115).

An additional drug used in preemptive treatment is cidofovir. The pharmacokinetic characteristics of cidofovir require its administration once a week (149). Although its main side effect is renal toxicity, this can be reduced by receiving hydration and probenecid (115). Cidofovir is often administered when ganciclovir or foscarnet treatment has been ineffective or if the patient demonstrates intolerance (149).

Letermovir (LET) is a novel antiviral drug that suppresses the CMV-terminase complex instead of CMV deoxyribonucleic acid polymerase (150). It can significantly decrease the incidence of CMV infection with few side effects and demonstrates no cross-resistance with other CMV antivirals (150). LET is available both orally and intravenously at 480 and 240 mg dosages, and was approved for use in CMV infection prophylaxis in CMV-seropositive recipients of allogeneic HSCT over the age of 18 in 2017 (151). Previous studies have demonstrated that LET resistance is primarily a result of mutations in the CMV UL56 gene (152,153).

Recently, clinical trials assessing the effectiveness and safety of novel drugs against CMV have been performed or are currently underway (Table II).

Brincidofovir is an orally administered drug that is a bioavailable lipid conjugate of cidofovir (154). Its antiviral effect has been confirmed both *in vivo* and *in vitro* (155-157). It has demonstrated a broad spectrum of effects on several viruses, including herpes virus, polyoma virus, adenovirus, papilloma virus and smallpox virus (158,159). The long half-life of brincidofovir and the absence of nephrotoxicity also makes it a desirable candidate for anti-CMV treatment (160-164). However, Marty *et al* (165) indicated that brincidofovir may be associated with gastrointestinal reactions following administration (165). Based on the existing research currently available, a complete evaluation cannot be made for the clinical application of brincidofovir.

Maribavir is a novel antiviral drug that has recently been developed (84). Despite potentially causing gastrointestinal toxicity, it can be administered orally without the adverse effects of nephrotoxicity and myelosuppression (166). Papanicolaou *et al* (166) reported that 400 mg maribavir administered twice daily can achieve similar effects to valganciclovir for the treatment of CMV viremia. However, undesirable results were obtained during maribavir phase two clinical trials (167). This negative result may have occurred due to many reasons, such as insufficient dose of maribavir (minimum dose was 100 mg twice daily), exclusion of high-risk groups, high sensitivity of PCR and low CMV-related diseases morbidity in the control group (168). Clinical data regarding the use of maribavir as treatment for refractory or drug resistant CMV have emerged (158,169-171); however, additional studies assessing maribavir administration for transplant recipients are required (158,169-171).



Table III. CMV-specific T cell therapy clinical trials.

Year	Type of T cell selection	Number of patients enrolled	Presentation of antigen	CMV outcome	GVHD status	(Refs.)
1995	<i>Ex vivo</i> expansion	14	Dendritic cells with CMV-infected fibroblasts; only CD8 clonal population infused	14 cleared CMV	3 developed grade I/II aGVHD (using steroids)	(176)
2002	<i>Ex vivo</i> expansion	7	CMV lysate and peptide mixes of pp65	1 with persistent CMV viremia, 1 with reactivation after using steroids, 6 with CMV-specific T cell expansion	None	(190)
2003	<i>Ex vivo</i> expansion	16	Dendritic cells with CMV-infected fibroblasts	2 developed CMV reactivation, 8 cleared CMV with antiviral treatment	3 with grade I aGVHD	(178)
2005	<i>Ex vivo</i> expansion	25	CMV antigen; only CD4 clonal population infused	7 developed CMV reactivation, 5 had CMV diseases, 2 died due to CMV	1 with GVHD	(191)
2007	<i>Ex vivo</i> expansion	9	Dendritic cells with peptide mix (pp65)	2 developed CMV reactivation, with no need of treatment	3 developed grade III aGVHD, 2 of them died; 2 with cGVHD	(188)
2010	IFN- $\gamma$ capture	18	pp65 protein	4 died associated with CMV, 15 developed <i>ex vivo</i> expansion	1 with GVHD	(175)
2011	IFN- $\gamma$ capture	18	Peptide mixes of pp65	11 with reactivation	3 with grade I aGVHD, 3 with grade II/III aGVHD, 3 with cGVHD	(187)
2011	Streptamer-selection	2	PBMCs with pp65-HLA beads	All cleared CMV	None	(187)
2012	<i>Ex vivo</i> expansion	7	Dendritic cells with peptide mixes (pp65, IE1)	4 cleared CMV, 2 with reactivation, 1 with transient increase in CMV PCR	None	(184)
2015	<i>Ex vivo</i> expression	16	Dendritic cells with peptide mix (pp65)	14 cleared CMV	None	(185)
2017	<i>Ex vivo</i> expression	37	PBMCs pulsed with pepmix spanning a variety of antigens	6 with CR, 10 PR	5 with grade I/II aGVHD, 1 with grade III	(181)
2018	CliniMACS Prodigy Cytokine Capture System	3	Virus-specific T-cell separation (CMV pp65 pepTivator)	2 cleared CMV, 1 with upload of CMV	None	(182)

CMV, cytomegalovirus; GVHD, graft vs. host disease; IFN, interferon; pp65, phosphoprotein 65; IE, immediate early protein; PBMCs, peripheral blood mononuclear cells; CR, complete response; PR, partial response.

*Treatment of refractory CMV infection.* Refractory CMV infection occurs when CMV antigenemia or DNAemia

remains positive, or the CMV DNA copy number increases or remains unchanged after 14 days of regular antiviral



treatment. When suspected resistance occurs, blood samples should be obtained from patients and sent for the phenotypic testing of resistance genes (1). In addition, certain antiviral drugs, including foscarnet sodium, should be replaced in the case of ganciclovir resistance. Ganciclovir administered in combination with phosphonate sodium is a method. The dose of ganciclovir may be occasionally increased to 15 mg/kg/d<sup>1</sup>, with G-CSF administered as a supportive treatment (13). Avery *et al* (172) demonstrated that the administration of oral maribavir may be beneficial for the treatment of refractory or resistant CMV infection. In addition, several case reports assessing the antimalarial drug, artesunate, and the novel anti-rheumatic drug, leflunomide, revealed that each agent successfully treated refractory CMV infections that were resistant to multiple antiviral drugs (173,174).

**Cellular immunotherapy.** The restoration of the CMV-specific CTL response in patients receiving transplantation is indispensable (175). Reusser *et al* (49) assessed the transfer of CMV-specific CD8<sup>+</sup> T cells for the first time in 1991 (49). Since then, many studies have done the same. Walter *et al* (176) selected 14 patients with CMV-specific CTL deficiency following allo-HSCT and applied CTL clones as treatment. The results confirmed the safety and efficiency of this immunotherapeutic technique (176). In a phase two clinical trial performed in 2013, Blyth *et al* (177) revealed that the adoptive transfer of CMV-specific CTL was exceedingly beneficial for the antiviral response exhibited by patients, the inhibition of virus replication and the spread of infection. Furthermore, Peggs *et al* (178) treated 16 patients with CMV infection following allo-HSCT with CMV-CTL. The results revealed that 50% of patients achieved negative CMV DNA without antiviral treatment (178). In a phase I/IIa trial, Neuenhahn *et al* (179) reported that the adoptive transfer of stem cells from a donor or third-party donor was associated with the reconstitution of CMV-specific T-cells in transplant recipients. In addition, the first application of virus specific T-cell transfer in Turkey exerted a degree of control over CMV replication (176). However, antiviral drugs may be administered in combination due to their lack of effect on CMV specific IgG (180).

The application of CMV-CTL can speed up the immune reconstruction of patients following allo-HSCT (181,182), effectively suppressing CMV replication whilst decreasing the use of antiviral drugs and their accompanying adverse reactions (183). It may therefore be an ideal replacement for antiviral drugs in the future (184,185). The occurrence of GVHD (both acute and chronic) is a significant concern in initial trials that utilize unmanipulated donor products (183). According to previous studies, these concerns can be eliminated with the development of technologies that select and expand specific T cells (179,186). Recently, the rates of GVHD following cell therapy have not exceeded those expected for patients post-HSCT (179,186). Almost all patients who develop GVHD following treatment do so as the result of other high-risk factors, including history of chronic or acute GVHD, subtherapeutic immunosuppression or receiving prior T cell-replete grafts (187-189) (Table III). However, there are still several challenges for the clinical application of this method (190). Although a study has suggested that G-CSF can

be used for stimulation (191), it is unknown how to practically prepare T cells for this treatment (192). In addition, there is no uniform standard for T-cell subsets that are optimal for anti-CMV treatment (186). Thus, this method needs to be improved through subsequent research.

Mesenchymal stem cells (MSCs) are one of the most common adult stem cells, originating from non-hematopoietic stem cells isolated from bone marrow (193). MSCs participate in the formation of the bone marrow hematopoietic microenvironment and provide significant support for the proliferation and differentiation of hematopoietic stem cells (194). MSCs can also support hematopoietic reconstitution by cell-cell contact and the secretion of cytokines to promote the shift from Th2 to Th1 phenotypes, increasing the expression of T regulatory cells to regulate the immune system (195). MSCs have been used in the treatment of GVHD and have wide application prospects (196). However, research on MSCs has primarily focused on its effect on allogeneic T cells (197). Thus, whether virus-specific T cells have the same effect is yet to be fully elucidated. In addition, little is known about how MSCs affect CTLs and the conversion of memory and effector T-cell subgroups in CMV-CTL. In our previous study, it was demonstrated that MSCs inhibit the proliferation of allogeneic CD8<sup>+</sup> T cells and CMV-specific T cells *in vitro* (198). However, there is insufficient evidence on whether its molecular mechanism of action and T-cell immune function are affected.

## 8. Leukemia relapse following allo-HSCT

Although CMV infection can cause high mortality following transplantation, Elmaagacli *et al* (199) revealed that patients with acute myeloid leukemia (AML) demonstrating donor and recipient CMV seropositivity or early or late post-transplantation CMV antigenemia have a decreased risk of relapse. This may be due to the apoptosis of AML cells following HCMV reactivation (200-203). However, current conclusions and related mechanisms require further research.

## 9. Conclusions

With the continuous advancement of transplantation technology, an increased number of patients with hematological tumors are undergoing HSCT. Correspondingly, the number of CMV infections following transplantation is also increasing. Antiviral treatment still occupies the mainstream position in the prevention and treatment of CMV, and drugs currently used for prophylaxis and preemptive treatment include ganciclovir, valganciclovir, foscarnet and cidofovir. Although the application of post-transplantation CMV infection antiviral prophylaxis and preemptive therapy has significantly decreased the risk of post-transplant CMV infection and disease, adverse reactions are commonplace. Thus, other methods that decrease the incidence of CMV infection and disease following transplantation are urgently required. Notable advancements have been established in recent years, including the elucidation of novel drugs, the adoptive transfer of CMV-specific CTLs and the application of MSCs. Although the effectiveness of these novel methods has not yet been determined, it is believed that with the progress of research, the prophylaxis and treatment

of CMV infection following transplantation will further improved.

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## Availability of data and materials

Not applicable.

## Authors' contributions

XZ, NJ and BC were responsible for confirming the topic, and collecting and analyzing the data. XZ designed and drafted the initial manuscript, and edited the figure legends and tables. All authors have read and approved the final manuscript.

## Ethics approval and consent to participate

Not applicable.

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## Competing interests

The authors declare that they have no competing interests.

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