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Review Article

Cytomegalovirus resistance in transplant patients Review

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Transplant patients therapy overview

CMV is a major cause of disease and mortality in patients undergoing Solid Organ Transplants (SOT) and Hematopoietic Stem Cell Transplants (HSCT). In SOT, CMV infection usually establishes itself in the first three months after transplantation in patients who do not receive prophylaxis. After this period, infection may occur in those who received prophylaxis. This infection affects around 30% to 50% of patients. Lung, small intestine, and pancreas transplants have been found to have the highest risks of CMV disease, while kidney and liver recipients have a lower risk. The greatest risk occurs when the recipient does not have IgG antibodies to CMV (R-) and receives an organ from a donor with positive IgG antibodies to CMV (D+), leading to "de novo" infection of the recipient due to primary exposure to the virus. Another common risk factor is when the recipient is CMV positive (R+) but is under intense cellular immunosuppression, which favors viral reactivation. Additionally, the use of highly immunosuppressive regimens and anti-lymphocyte therapy (such as thymoglobulin), especially to treat rejection, are risk factors for CMV disease. Rejection itself can stimulate CMV reactivation, and the decrease in lymphocytes caused by anti-lymphocyte therapy increases the probability of viremia and, consequently, the associated disease.

In the case of HSCT, before the widespread use of antiviral strategies, CMV was one of the main causes of death in these patients. Approximately a quarter of patients developed CMV disease, and of those, 80% died due to virus-associated pneumonia. At that time, diagnostic methods were not very sensitive and results were obtained too late for the clinical situation at hand. However, currently, with the use of aggressive and timely antiviral therapies, and monitoring with more sensitive and rapid virological techniques, as well as options for universal prophylaxis or early therapy, the frequency of CMV disease has decreased significantly, reaching about 3.5% to 10% by day 100 after transplant. In the case of recipients who have already been previously infected with CMV and who will undergo immunosuppression during transplantation, the risk of CMV reactivation from the latent phase is greater. For recipients who are CMV positive (+), receiving a transplant from a donor who is CMV negative (-) or CMV positive (+) poses a potential risk of CMV reactivation in the recipient or reinfection with the strain of the donor. This situation should be actively monitored, as it is likely to occur eventually. Factors that increase this risk include intense immunosuppressive therapies, the type of HSCT (in descending order: umbilical cord, unrelated donor, peripheral cells, bone marrow), and Graft Versus Host Disease (GVHD) [1].

Currently, there are two therapeutic strategies used to prevent the development of CMV disease in transplant patients:

Universal prophylaxis: This strategy involves administering an antiviral, such as valganciclovir, to all patients after transplant. In the case of SOT, this strategy is applied to high-risk patients, such as those CMV seronegative recipients receiving organs from CMV seropositive donors, lung or intestinal transplant recipients, or CMV seropositive recipients undergoing immunosuppressive treatment with agents that eliminate T lymphocytes.

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Pre-emptive Treatment: Involves directing prophylaxis only toward high-risk transplantation recipients (e.g., patients in whom early replication of CMV occurs) in an attempt to prevent the progression of asymptomatic infection into CMV disease. This strategy involves administering the antiviral only to those patients who reach a certain level of CMV viremia. In the context of HSCT, this strategy is universally used in CMV seropositive patients with intermediate or low risk, while in SOT it is used only in cases of CMV seropositive patients with low risk. It is based on monitoring viral load using real-time PCR, where patients are treated when CMV DNA levels in whole blood exceed a specific threshold, and treatment is stopped once the viral load is reduced to levels undetectable [2].

Antivirals, mechanism of action, and development of resistance

Currently, limited therapeutic options for treating or preventing CMV disease in transplant recipients are available. As of September 2021, only five drugs are FDA-approved for systemic use for treating or preventing CMV disease: letermovir, ganciclovir and valganciclovir, foscarnet and cidofovir https://www.fda.gov/media/152713/download and two months later the list included marivabir for a common type of post-transplant infection that is resistant to other drugs.

Therapy involves the sequential use of Ganciclovir (GCV), Foscarnet (FOS) and Cidofovir (CDV), usually in that order and sometimes in combination. The introduction of oral valganciclovir has strengthened the position of ganciclovir as the preferred treatment in the first instance [3,4]. These antivirals have limited therapeutic efficacy due to their moderate antiviral activity, low bioavailability, emergence of resistance, and possible toxic effects associated with their use [5].

In the last two decades, great success has been achieved in the prevention of morbidity and mortality caused by CMV by using ganciclovir, in prophylaxis or preventive treatment strategies. However, in a small percentage of cases, this strategy is not successful when antiviral therapy is insufficient to stop viral replication. So continued and persistent replication of CMV, along with prolonged exposure to antivirals (usually for months), over time can lead to the accumulation of antiviral resistance mutations, ultimately conferring resistance to antivirals. In 2017, the FDA approved the use of Letermovir for CMV prophylaxis in HSCT [6]. In a phase III clinical trial, it was found that prophylaxis with letermovir led to a notable decrease in the risk of CMV infections, and no observed toxic effects related to myelosuppression, renal or hepatic dysfunction [7].

GCV is a guanosine analog that contains an acyclic ribose moiety. GCV was the first potent and effective therapy developed for CMV disease, and its selective antiviral activity depends on its initial phosphorylation by the UL97 kinase. Once phosphorylated by CMV UL97 kinase, it is converted to triphosphate by cellular enzymes. This triphosphate inhibits viral DNA polymerase. The other two classic antivirals, FOS and CDV, do not require initial modification by a viral enzyme. However, CDV is converted to diphosphate by cellular enzymes.

A 5% - 10% incidence of ganciclovir-resistant viruses has been frequently reported, and this is sometimes associated with progressive or fatal CMV disease. Resistance is most common after lung and kidney-pancreas transplants. Cases of rapid emergence of GCV resistance within just a few weeks after initiating treatment, as well as late antiviral-resistant CMV disease after stopping preventive therapy, have also been reported.

The CMV UL97 gene encodes amino acid sequence motifs characteristic of protein kinases and is an appropriate target for antivirals due to its essential role in normal viral replication. UL97 plays a prominent role in the action of two important CMV antivirals, ganciclovir and Maribavir (MBV). MBV is a potent UL97 kinase inhibitor. Mutations in UL97 are an important mechanism of CMV resistance to both antivirals. Various mutations have been discovered in the UL97 gene, as well as combinations of mutations, which can confer variable levels of resistance to the MBV drug (V353A, T409M, H411L, H411N, and H411Y) [4].

In the vast majority of cases, ganciclovir resistance in CMV is based on seven common amino acid substitutions in the UL97 kinase. These replacements include M460V/I, H520Q, C592G, A594V, L595S and C603W. These mutations have been identified as resistance markers and are used for the diagnosis of ganciclovir resistance. However, it has also been observed that there are less common mutations in the UL97 kinase, which are grouped in codons 590 to 607, which may be involved in resistance to ganciclovir in some cases [8].

Mutations in the CMV DNA polymerase UL54 gene have been associated with resistance to traditional polymerase inhibitors such as ganciclovir, foscarnet, and cidofovir. Several mutations grouped in certain functional domains of DNA polymerase have been observed, each with characteristic resistance phenotypes. New mutations that may have an impact on the response to treatment continue to be identified and reported periodically [8]. It is possible to select mutations in the UL54 gene that result in cross-resistance between GCV and CDV and between GCV and FOS. In addition, there are mutations that can confer resistance to multiple antivirals. These mutations in the UL54 gene usually occur because of prolonged exposure to antivirals. Furthermore, the combination of mutations in the UL97 and UL54 genes may result in higher levels of resistance to GCV [4].

Following the continuous emergence of resistance mutations, various pharmacological alternatives for CMV have been further investigated. The viral terminase complex, composed of the UL56, UL89, and UL51 genes, plays an essential role in cleaving and packaging unit-length viral genomes into the viral capsid after DNA replication using a rolling circle template [9]. This terminase-related drug target has been explored in several drug discovery programs and an antiviral drug called letermovir was developed. In vitro studies have shown that the viral mutations responsible for letermovir resistance are mainly found in the UL56 component. Additional experiments have also revealed the occasional occurrence of mutations in UL89.

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Furthermore, it has been observed that the third component of the terminase, UL51, can also present mutations. The diagnostic relevance of the UL51 mutation lies in its ability to enhance letermovir resistance of certain UL56 mutations at a relatively low adaptive cost. This suggests that the presence of the UL51 mutation may amplify letermovir resistance, even in the presence of other UL56 mutations, with significant clinical impact [10].

At the same time, in addition to UL97 resistance to MBV has been attributed to the UL27 gene, which encodes a viral nuclear protein [11]. Compensatory mutations in UL27 have been observed to arise when UL97 kinase activity is inhibited by MBV. These mutations appear to counteract the loss of kinase function and result in low-level resistance to the drug [12].

The clinical significance of UL27 mutations that confer low-level resistance is not yet clearly established. However, by allowing continued virus replication in the presence of MBV, these mutations could facilitate the emergence of additional mutations that, either individually or in combination with the pre-existing mutation, lead to increased resistance to MBV [13].

Alternative drugs such as Leflunomide and Artesunate are still in the study. Leflunomide is a cheap and easily available anti-rheumatoid arthritis drug that has been shown to have anti-CMV properties both in vitro and in vivo although its efficacy seemed sub-optimal. Artesunate is an inexpensive antimalarial agent and has been sporadically reported in the literature to be effective in CMV reactivation in patients who are intolerant or resistant to ganciclovir. However, its efficacy should be explored prospectively in settings where ganciclovir cannot be used and access to other CMV-active drugs is limited.

Methods for detecting antiviral resistance

In clinical practice, it is essential to perform laboratory tests to confirm the presence of antiviral-resistant cytomegalovirus, since many cases of viral persistence during treatment are not associated with viral resistance to antivirals [3]. Since viral isolation in cell culture is uncommon in current diagnostic laboratory practice and susceptibility testing of clinical cytomegalovirus isolates is not readily available in a timely manner, it has become common to resort to genotypic testing as the primary method for detecting antiviral resistance. Detection of mutation associated with resistance justifies the choice of an alternative therapy [8].

The key steps are CMV DNA extraction isolation from clinical samples, PCR amplification of specific regions of the CMV genome, sequencing of the viral DNA, comparison with reference sequences, identification of mutations, and their correlation with known resistance to the antivirals. Furthermore, in some cases, functional validation may be performed to demonstrate that the identified mutations confer resistance [14].

The current standard method for cytomegalovirus Antiviral Resistance (AVDR) genotyping is Sanger sequencing, which has the ability to detect mutations present in more than 20% of the viral subpopulation. However, with advances in sequencing technology, Next-Generation Sequencing (NGS) has been evaluated as a more sensitive approach to detecting AVDR mutations. NGS technology has been reported to show high concordance with Sanger sequencing and has identified additional mutations not previously detected with Sanger sequencing.

Despite its advantages, it has not yet been routinely adopted in clinical laboratories due to the need for technical expertise, a prolonged turnaround time compared to Sanger sequencing, and interpretive challenges requiring complex analysis and use of specialized bioinformatics platforms [15] (Table 1).

Table 1: Mutations conferring resistance to antivirals.

Gene	Mutation	Antivíral	Resistance Level
UL27	A269T [16]	Maribavir	Low
UL27	L193F [17]	Maribavir	Low
UL27	L355P [18]	Maribavir	High
UL27	V353E [16]	Maribavir	Low
UL27	W362R [18]	Maribavir	Low
UL51	P91S [10]	Letermovir	Low
UL54	A505V [19]	Cidofovir	Low
UL54	A809V [20]	Ganciclovir Foscarnet	Low High
UL54	A834P [17]	Ganciclovir Cidofovir Foscarnet	High Middle High
UL54	A987G [21]	Ganciclovir Cidofovir	High High
UL54	C539G [8]	Ganciclovir Cidofovir	Middle Middle
UL54	C539R [22]	Ganciclovir Cidofovir	Middle High
UL54	D413A [13]	Ganciclovir Cidofovir	High High
UL54	D413E [23]	Ganciclovir Cidofovir	Middle Middle
UL54	D413N [8]	Ganciclovir Cidofovir	Middle High
UL54	D515E [24]	Ganciclovir Foscarnet	Low Middle
UL54	D515Y [25]	Ganciclovir Foscarnet	High Middle
UL54	D542E [26]	Cidofovir	High
UL54	del981-2 [17]	Ganciclovir	High
UL54	E756D [20]	Foscarnet	Middle
UL54	E756K [20]	Ganciclovir Cidofovir Foscarnet	Low Low High
UL54	E756Q [27]	Foscarnet	Middle
UL54	F412L [20]	Ganciclovir Cidofovir	Middle High
UL54	F412S [28]	Ganciclovir Cidofovir	High High
UL54	F412V [8]	Ganciclovir Cidofovir	Middle High
UL54	F595I [17]	Foscarnet	Low
UL54	G841A [17]	Ganciclovir Cidofovir Foscarnet	Middle Low Middle
UL54	G841S [19]	Ganciclovir Foscarnet	Low Low

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UL54	I521T [24]	Ganciclovir Cidofovir	Low High
UL54	I726T [19]	Ganciclovir	Low
UL54	K500N [22]	Ganciclovir Cidofovir	Middle Middle
UL54	K513R [8]	Ganciclovir Cidofovir	Middle High
UL54	L516W [29]	Ganciclovir Cidofovir	Middle High
UL54	L516R [13,44]	Ganciclovir Cidofovir	High High
UL54	L545S [12]	Ganciclovir Cidofovir	Middle High
UL54	L545W [20]	Ganciclovir Cidofovir	Middle High
UL54	L773V [8]	Ganciclovir Cidofovir Foscarnet	Middle Low Middle
UL54	L802M [30]	Ganciclovir Foscarnet	Middle Middle-High
UL54	L957F [22]	Ganciclovir	Low
UL54	M844T [20]	Foscarnet	Low
UL54	M844V [20]	Ganciclovir Foscarnet	Low Low
UL54	N408K [20]	Ganciclovir Cidofovir	Middle High
UL54	N408D [8]	Ganciclovir Cidofovir	Middle Middle
UL54	N495K [31]	Foscarnet	Middle
UL54	P488R [22]	Ganciclovir Cidofovir	Middle High
UL54	P522S [8]	Ganciclovir Cidofovir	Middle Middle
UL54	P829S [22]	Ganciclovir	Low
UL54	Q578H [21]	Ganciclovir Cidofovir Foscarnet	Middle Low Middle
UL54	Q578L [19]	Ganciclovir Foscarnet	Low Middle
UL54	S585A [17]	Foscarnet	Low
UL54	T552N [22]	Ganciclovir Foscarnet	Low Low
UL54	T700A [32]	Foscarnet	Middle
UL54	T813S [20]	Ganciclovir Cidofovir Foscarnet	Low Low Middle
UL54	T821I [33]	Ganciclovir Cidofovir Foscarnet	Middle Low High
UL54	T838A [31]	Foscarnet	Low
UL54	V526L [3]	Ganciclovir Cidofovir	High Low
UL54	V715A [29]	Foscarnet	Low
UL54	V715M [8]	Foscarnet	High
UL54	V781I [20]	Ganciclovir Foscarnet	Middle Middle-High
UL54	V787A [25]	Cidofovir Foscarnet	Low Middle
UL54	V787E [34]	Ganciclovir Cidofovir Foscarnet	High Low Middle
UL54	V787L [22]	Ganciclovir Foscarnet	Low Middle
UL54	V812L [22]	Ganciclovir Cidofovir Foscarnet	Low Middle Low
UL54	V946L [22]	Foscarnet	Low
UL56	A365S [35]	Letermovir	Low
UL56	C25F [35]	Letermovir	High
UL56	C325F [35]	Letermovir	High
UL56	C325R [35]	Letermovir	High
UL56	C325W [35]	Letermovir	High
UL56	F261C [35]	Letermovir	Middle
UL56	K258E [35]	Letermovir	High
UL56	L254F [35]	Letermovir	Middle
UL56	L257I [35]	Letermovir	Middle
UL56	L328V [35]	Letermovir	Low
UL56	N232Y [35]	Letermovir	High
UL56	N368D [35]	Letermovir	Low
UL56	R369G [35]	Letermovir	High
UL56	T244K [35]	Letermovir	Middle
UL56	V231A [35]	Letermovir	Low
UL56	V236A [35]	Letermovir	Low
UL56	V236L [35]	Letermovir	High
UL56	Y321C [35]	Letermovir	Middle
UL89	D344E [6]	Letermovir	High
UL89	N329S [6]	Letermovir	Low
UL89	T350M [6]	Letermovir	Low
UL97	A594E [36]	Ganciclovir	Middle
UL97	A594V [17]	Ganciclovir	High
UL97	A613V [37]	Ganciclovir	Low
UL97	C480F [21]	Maribavir Ganciclovir	High Low
UL97	C480R [38]	Maribavir Ganciclovir	High High
UL97	C518Y [39]	Ganciclovir	High
UL97	C592G [40]	Ganciclovir	Low
UL97	C603R [36]	Ganciclovir	High
UL97	C603S [36]	Ganciclovir	Low
UL97	C603W [17]	Ganciclovir	High
UL97	C607F [41]	Ganciclovir	Low
UL97	C607Y [8]	Ganciclovir	High
UL97	D456N [38]	Maribavir Ganciclovir	High High
UL97	E596G [42]	Ganciclovir	Low
UL97	E596Y [24]	Ganciclovir	High
UL97	F342S [40]	Maribavir Ganciclovir	High High
UL97	F342Y [21]	Maribavir Ganciclovir	Low-Middle High
UL97	H411N [17]	Maribavir	High
UL97	H411Y [43]	Maribavir	High
UL97	H411L [13,44]	Maribavir	High
UL97	H520Q [17]	Cyclopropavir Ganciclovir	High High
UL97	I610T [24]	Ganciclovir	Low
UL97	K359E [40]	Ganciclovir	Middle
UL97	K359Q [40]	Ganciclovir	Middle
UL97	L337M [13]	Maribavir	Middle
UL97	L397R/I [44]	Ganciclovir	High
UL97	L405P [36]	Ganciclovir	Low
UL97	L595S [19]	Ganciclovir	High
UL97	L595W [17]	Ganciclovir	High
UL97	M460I [17]	Cyclopropavir Ganciclovir	High High
UL97	M460T [36]	Ganciclovir	High
UL97	M460V [20]	Cyclopropavir Ganciclovir	Middle High
UL97	P521L [45]	Maribavir Ganciclovir	High High
UL97	T409M [46]	Maribavir	High
UL97	V356G [40]	Maribavir Ganciclovir	High High
UL97	V466G [40]	Maribavir Ganciclovir	High High
UL97	Y617del [38]	Maribavir Ganciclovir	High High

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