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New advances in the management of cytomegalovirus in allogeneic haemopoietic stem cell transplantation

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Abstract

Cytomegalovirus (CMV) viraemia continues to be a frequent complication in the post-haemopoietic stem cell transplantation period despite a low incidence of CMV end-organ disease. Several significant advances in the understanding and management of CMV infection have occurred in the last few years including improved diagnostics, monitoring of CMV immunity, availability of novel anti-CMV drugs, and emerging use of immunotherapies including CMV-specific T-cell infusions. In addition to reviewing these advances we also explore some of the more practical prescribing issues of the older and newer CMV drugs including cost, toxicity and drug interactions to help clinicians navigate this new era of CMV management.

Introduction

Cytomegalovirus (CMV) infection is the most frequent infectious complication following allogeneic haemopoietic stem cell transplantation (HSCT) and is associated with adverse transplant outcomes and additional healthcare costs.[1] Significant advances in the management of CMV have occurred in recent years, including improvements in viral load monitoring (with the use of international standards for assay comparison), immune monitoring diagnostics such as interferon gamma release assays, new antiviral treatments with novel mechanisms of action such as terminase inhibitors (letermovir) and direct kinase inhibitors (maribavir), and the emerging use of CMV-specific T-cell therapies (summarised in Table 1). In this review we evaluate these changes and provide an updated overview for clinicians managing CMV infection in allogeneic HSCT.

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Epidemiology

The CMV allograft landscape is changing. Currently two-thirds of all seropositive HSCT recipients will develop CMV viraemia in the post-transplant period with the most important risk factor being pre-transplant recipient and donor CMV serostatus.[2] Pre-transplant recipient and/or donor CMV seropositivity is also associated with reduced

Table 1 Summary of advances in CMV management in HSCT

	Key points	
Epidemiology	• Rates of CMV disease have reduced but CMV viraemia is unchanged • Gastrointestinal CMV disease is now most frequently seen • Delayed CMV viraemia, multiple reactivation, prolonged duration of viraemia are observed with changes in HSCT regimens and with GVHD • CMV viraemia is associated with higher transplant mortality, ICU outcomes, increased cost and increased fungal infections	
Diagnostics	• Change to standardised testing with CMV viral loads measured in international units/mL • Whole viral genome sequencing availability for resistance mutations • CMV immune monitoring to measure CMV-specific T cells may guide treatment	
Drugs	Prophylaxis • Letermovir shown to be very effective for prophylaxis with reduced overall mortality at 24 weeks	Treatment • Maribavir prophylaxis failed to prevent CMV tissue infection but is currently under study for refractory CMV viraemia and resistant CMV
Immunotherapy	Prophylaxis • Donor-derived CMV T cell prophylaxis reduces severity of CMV infection and requirement for CMV therapy • Prophylactic third party CMV T-cell therapies are being evaluated	Treatment • Donor-derived CMV T cell treatment is effective treatment for viraemia and tissue infection • Third party partially HLA-matched CMV T cells are effective for recurrent viraemia

CMV, cytomegalovirus; GVHD, graft versus host disease; HSCT, haemopoietic stem cell transplantation; ICU, intensive care unit.

survival and increased transplant-related mortality compared with CMV seronegative pairs.[3] Other well established and emerging risk factors for CMV include graft versus host disease (GVHD), corticosteroid use, umbilical cord transplants, haploidentical transplants with post-transplant cyclophosphamide and T-cell depleted grafts.[4–6]

However, the increasing complexity and use of T-cell depleting conditioning regimens in HSCT have significantly impacted on the timing and kinetics of CMV viraemia in the post-transplant period.[1] CMV reactivation is no longer confined to the early post-HSCT period (<100 days) but may occur months later and with multiple recurrences despite adequate treatment.[2] In addition, the effective use of universal CMV prophylaxis or pre-emptive therapy in recent years has resulted in a significant decline in CMV tissue invasive end-organ disease from approximately 30% to 5%.[1] Whereas CMV pneumonitis was once frequently seen, gastrointestinal CMV disease (colitis, ileitis, gastritis) now constitutes greater than 90% of clinical disease manifestations.[1] Finally, the development of multidrug-resistant CMV (up to 14.5% in high-risk transplants) and treatment refractory CMV has been found to impact significantly patient morbidity and mortality.[7]

Burden of CMV viraemia

The majority of patients with CMV infection will develop CMV viraemia without disease, most commonly due to reactivation of latent virus in the patient. There is a 1.8–2.6 times increased risk of death within the first 12 months of HSCT in patients developing CMV viraemia compared with no viraemia with an impact seen even with relatively low levels of viraemia.[1] HSCT recipients requiring admission to an intensive care unit (ICU) have a 5.7 times increased risk of death at 12 months if they had CMV reactivation compared with no reactivation.[8] The management of CMV viraemia is further complicated by potential treatment toxicities (e.g. ganciclovir-induced neutropenia, nephrotoxicity),[9] prolonged hospitalisation,[10] worse ICU outcomes,[8] increased risk for other bacterial or fungal infections,[11] increased healthcare costs[10] and contribution to transplant-related mortality.[1] Overall, it is estimated that the attributable healthcare cost of managing CMV is US$58 000–74 000 per patient, placing a large economic burden on over stretched healthcare resources.[10]

Laboratory testing of CMV

Laboratory testing for CMV is performed prior to and after HSCT (see Table 2). Such testing aims to (i) establish serostatus of donor/recipient, (ii) detect presence of viral copies using nucleic acid testing (NAT) of plasma, whole blood and/or tissue (iii) assess antiviral resistance in patients failing antiviral therapy, (iv) utilise biomarkers such as CMV-specific T-cell immunity to assess risk of reactivation and (v) for therapeutic drug monitoring (TDM) to assess antiviral levels in blood, particularly in patients failing therapy.

Nucleic acid tests are the most commonly used method to diagnose CMV infection and can be performed on blood (whole blood and plasma), fluids (cerebrospinal and vitreous) and tissue samples (including colonic tissue, bronchoalveolar lavage (BAL) and brain tissue). Both qualitative and quantitative assays are performed using standardised commercial assays with viral loads now reported in standardised form as

Table 2 Laboratory testing for cytomegalovirus (CMV)

Technique	Summary
Viral load – nucleic acid test	Detect and quantitate CMV DNA in whole blood or plasma, sterile fluids and tissue Provides viral loads (viral copies/mL and standardised as IU/mL)
Serology	Indicates past exposure to CMV
Immunohistochemistry	Detection of invasive CMV in tissue specimens using antibodies to viral proteins for detection of viral transcription
Drug resistance	Genotyping to detect known mutations in UL97, UL54 and UL56 genes for drug resistance
Therapeutic drug monitoring	Monitoring of ganciclovir and other drug levels
CMV immunity	Quantiferon-CMV or CMV ELISpot assays to assess CMV T-cell immunity, tetramer staining of peripheral blood to detect T cells directed to specific HLA-bound CMV peptides

HLA Human leukocyte antigen.

international units per millilitre (IU/mL) against a World Health Organisation (WHO) standard.[12] Laboratories should be enrolled in quality assurance programmes with results calibrated to the WHO international standards in order to improve the interpretation of quantitative results from different testing laboratories.[12] NAT testing on blood/plasma is generally performed weekly from early post-transplant to approximately day 100 or later post-HSCT in patients with active GVHD on immunosuppression.

Definitive diagnosis of CMV organ disease remains dependent on proven histological evidence of viral tissue invasive effects such as presence of viral inclusion bodies or positive CMV immunohistochemistry staining.[13] A blood viral load >5000 IU/mL correlates with an increased likelihood of CMV disease in HSCT recipients.[14] A crucial observation, however is that CMV disease can occur in a tissue-tropic manner, being present only in some tissue compartments. Substantial differences in viral loads levels in affected tissues and levels in blood have been observed.[15] Thus the presence of low or undetectable viral loads in blood does not exclude organ-specific CMV disease, particularly in gastrointestinal and eye disease.[15] The detection of CMV DNA in BAL and colonic tissue can occur without end-organ disease, and may represent pulmonary viral shedding or DNA contamination from blood. A recent study determined that a CMV BAL DNA cut-off of 500 IU/mL differentiated between CMV shedding and CMV pneumonia (>500 IU/mL) in HSCT recipients.[13]

CMV immune monitoring

Post-transplantation monitoring of CMV immunity in addition to serial quantitation of CMV DNA may better identify patients at risk of CMV complications.[2,16,17] New advances in diagnostic assays to rapidly assess CMV-specific immunity include the Quantiferon-CMV assay (Qiagen, Hilden, Germany), the T-Track CMV ELISPOT (Lophius Biosciences GmbH, Regensburg, Germany) and the T-SPOT. CMV assays (Oxford Immunotec, Abingdon, U.K.).[17] These commercial assays have the advantage of real-time laboratory processing and methods for standardisation.

Studies of CMV immune monitoring in the HSCT population have shown clinical benefits in shortening antiviral treatment duration,[16] predicting recurrent CMV reactivation[2] and identifying patients at low risk of CMV complications or with lower CMV viral loads.[2,17] Identifying patients that have developed reconstitution of CMV-specific immunity using virological and immunological monitoring post-HSCT significantly reduced the duration of anti-CMV pre-emptive treatment by a median of 9 days.[16] HSCT recipients with inadequate reconstitution of CMV immunity at day +100 or at the end of first CMV reactivation were much more likely to experience recurrent CMV reactivation,[2] implying that the period for CMV monitoring should be extended. Further research is warranted to determine when to perform immune monitoring and how to assess its clinical impact, including the potential to reduce antiviral use or guide prophylaxis duration.

CMV resistance testing

Testing for CMV resistance may be indicated when recurrence of viraemia occurs after initial viral clearance or with failure to achieve >1 log10 decrease in CMV viral load after more than or equal to 2 weeks of full dose antiviral treatment.[18] For patients failing antiviral therapy, potential causes include virus mutation leading to antiviral pharmacological resistance or low therapeutic antiviral levels due to underdosing, increased metabolism and/or increased excretion. In the case of oral antivirals, reduced patient compliance or poor absorption particularly if GVHD is present should be considered. Resistance testing typically involves genotyping for UL97 phosphotransferase and UL54 polymerase genes or more recently whole genome sequencing, although the genotype and phenotype differ in some patients.[19]

Therapeutic drug monitoring

TDM facilitates optimal dosing of antivirals as therapeutic levels may vary depending upon renal function,

Table 3 Pharmacy

	Valaciclovir (2 g qid)	Ganciclovir	Valganciclovir	Foscarnet	Cidofovir	Brincidofovir	Letermovir	Maribavir
Major toxicities	Renal impairment+	Marrow suppression+++	Marrow suppression+++	Marrow suppression+; electrolyte imbalance+++; renal impairment++; GI++	Marrow suppression+; renal impairment+++	GI++	None	GI+
Relevant drug/drug interactions	Antidepressants, verapamil	None	None	None	None	None	Cyclosporine, tacrolimus, itraconazole, voriconazole, antidepressants, antiepileptics	None
Drug cost per week of prophylaxis (based on 75 kg patient with normal renal function)	$	$$	$$	$$$	N/A	Unknown – not available commercially	$$$	Unknown – not available commercially
Drug cost per week of induction therapy (based on 75 kg patient with normal renal function)	N/A	$$	$$	$$$	$$ (one dose)	Unknown – not available commercially	N/A	Unknown – not available commercially
Administration considerations	Oral, large pill burden	i.v., can be administered via a portable infusion pump as outpatient	Oral	i.v. infusion, pre-/post-hydration, electrolyte replacement essential	i.v. infusion with probenecid and pre-/post-hydration essential	Oral	Oral and i.v.	Oral only
Other considerations	Use for prophylaxis only with moderate efficacy	Cytotoxic manufacturing facilities required to make doses	Limited data in serum levels and doses for extreme weights. Lower absorption in gut GVHD. Dose on Crockroft-Gault calculated CrCl	Difficult to administer as outpatient due to pre-hydration and i.v. electrolyte replacement	SAS, cytotoxic manufacturing facilities required to make doses	No commercial access	SAS, prophylaxis only, no data in pre-emptive/treatment	No commercial access

+, minor; ++, moderate; +++, major. $, under 100 dollars; $$, 100–1000 dollars; $$$, over 1000 dollars. CrCl, creatinine clearance; GI, gastrointestinal; GVHD, graft versus host disease; i.v., intravenous; SAS, special access scheme.

particularly in the case of ganciclovir.[20] Dose adjustment based on population pharmacokinetics Bayesian prediction model has been demonstrated to optimise exposure in solid organ transplantation,[20] although a study of TDM in HSCT showed that immune status is more important than trough ganciclovir levels in predicting clearance of CMV during pre-emptive therapy.[21] TDM is not routinely available at present but can be performed in a research setting. Further research is warranted in HSCT recipients to optimise ganciclovir and valganciclovir dosage, and for use with novel antivirals where less is known about dose–response relationships.

Management of CMV viraemia

Most HSCT programmes have adopted a CMV pre-emptive strategy whereby frequent monitoring and the early detection of CMV virus at a threshold level triggers the commencement of anti-CMV treatment. CMV viraemia is usually an indication to start antiviral therapy, however the optimal viral load level at which to commence treatment is unknown, ranging between any detectable viral load to >1000 IU/mL.[5] The viral load at which pre-emptive treatment is commenced depends particularly on host immunosuppression, including conditioning regimen, use of T-cell depletion, known pre-transplant CMV serostatus and concomitant immunosuppression for acute GVHD.[5] Another important factor is the kinetics of CMV infection, with serial quantitation of viraemia to monitor disease progression and treatment responses to assess how much, and how rapidly viraemia is progressing.[14] Viral load changes <0.5 log10 are generally considered insignificant,[5] although clinical judgement should be used, particularly in highly immunocompromised patients. Monitoring for CMV viraemia is recommended for the first 100 days post-HSCT or longer if GVHD is present. However, this duration may need extending in patients at risk of late CMV reactivation, for example, T-cell depletion or following primary prophylaxis.

Currently, valganciclovir and ganciclovir remain the first line antiviral therapy of choice as pre-emptive or prophylactic therapy[9] (Table 3). The major disadvantages of these agents are myelosuppression (approximately 20–50% during induction therapy), the requirement for intravenous administration for ganciclovir, and development of resistance with long-term use.[7,19] Although valganciclovir, the oral prodrug of ganciclovir alleviates the requirement for intravenous therapy, dosing requires careful adjustment for renal function, as well as taking into consideration gut absorption, particularly in the presence of GVHD.[22] Some institutes use high dose valaciclovir as prophylaxis against CMV in high-risk seropositive umbilical cord transplants.[6]

Foscarnet is often used as a second line therapy following ganciclovir failure due to resistance, or adverse effects of ganciclovir, particularly myelotoxicity.[5] Inpatient admission is usually required due to the need for intravenous administration, the requirement for electrolyte replacement (particularly management of potassium, calcium and magnesium levels), the pre-/post-fluid required to prevent nephrotoxicity (occurring in up to 50% of patients),[23] and the need to monitor closely for adverse effects. Cidofovir is an alternative treatment option, but renal toxicity may limit its use. In a report of 126 HSCT patients treated with cidofovir (with probenecid), the risk of renal toxicity was 26%.[24] Most of the renal toxicity was mild (low-degree proteinuria or mild elevation of the serum creatinine), but some signs of renal impairment remained after drug discontinuation of cidofovir in approximately half of these patients. Cross-resistance occurs between cidofovir and foscarnet with ganciclovir, particularly with mutations in the UL54 gene.[19]

Novel anti-CMV drugs

Representing a significant advance in the field of CMV management in HSCT are several, novel, clinically effective and well-tolerated anti-CMV agents which may overcome some of the limitations and adverse effects outlined above (Table 1).

Letermovir

Letermovir is an anti-CMV-specific agent available in both oral and intravenous formulation with excellent *in vitro* CMV antiviral activity.[25] The mechanism of action is novel and involves targeting CMV viral terminase and preventing cleavage of DNA in the late stages of viral replication.[25] The drug is well tolerated with low rates of myelotoxicity and has been used successfully to treat drug-resistant CMV.[26] In a large phase III randomised study of 585 participants comparing letermovir as prophylaxis versus standard of care pre-emptive treatment, there was a significant reduction of CMV infection seen with letermovir compared to standard of care (37.5% vs 60.6%) at week 24.[25] In addition, all-cause mortality was observed to be lower in the letermovir group at week 24 (10.2% letermovir vs 15% standard of care, $P = 0.03$).[25]

Based on these results, letermovir was recently granted food and drug administration approval for primary CMV prophylaxis in HSCT in the United States. Yet, several clinical questions remain such as which priority HSCT groups would most benefit from letermovir prophylaxis, what is the efficacy of letermovir in the presence of CMV DNAemia and what is the optimal

duration of prophylaxis? It is also unclear what is the threshold to resistance, detected by mutations in UL56 and other genes encoding the terminase complex proteins including pUL89 and pUL51. A case of breakthrough CMV pneumonia occurring while on letermovir prophylaxis in a high-risk HSCT recipient was recently reported.[27] It is also noted that very high-risk HSCT recipients with early detectable CMV viraemia were excluded from the phase III study.[25] Cost of the drug to the healthcare system is also a concern as letermovir should aim to be cost-effective as well as clinically effective.

Letermovir is well tolerated but is only active against CMV. If broad anti-herpes simplex virus (HSV) and varicella zoster virus viral cover is required, then concomitant therapy with anti-herpes agents such as aciclovir or valaciclovir is required. Letermovir also has significant drug interactions that need to be considered especially in relation to cyclosporine. When used concurrently with cyclosporine the dose of letermovir is halved from 480 to 240 mg daily.[25] At the time of writing, letermovir is currently only accessible in Australia and many countries under the special access scheme.

Maribavir

Maribavir is a novel benzimidazole antiviral agent that is highly potent against CMV, including ganciclovir-resistant strains.[18] It directly targets the CMV protein kinase UL97 to inhibit effectively viral replication and encapsulation, with mutations in UL97 and UL27 resulting in resistance.[18] Further advantages with maribavir are the availability of an oral formulation and the appreciable lack of either myelotoxicity or nephrotoxicity.[18] The most commonly reported side-effects include metallic taste disturbance and headache.[18] In a small case series, maribavir was successful in clearing CMV virus in treatment refractory CMV disease, however, the development of maribavir resistance in one patient while on treatment is a concern.[28]

A large, randomised phase III study of 681 HSCT recipients comparing prophylactic strategies of maribavir to placebo failed to reach the primary end-point of preventing CMV disease at 6 months (4% maribavir vs 5% placebo).[9] Several explanations for these results include the use of low incident primary end-points such as CMV disease and the dosing regimen chosen for maribavir. Two large phase III studies (2018) evaluating maribavir as a pre-emptive agent compared to valganciclovir and in refractory or drug-resistant CMV compared to standard of care are currently recruiting.

Brincidofovir

Brincidofovir is the orally available lipid ester prodrug form of cidofovir showing much greater potency against CMV than conventional cidofovir but with much less nephrotoxicity due to its lipid formulation.[29] It has activity against HSV, adenovirus and BK virus in addition to CMV.[29] A phase III clinical study of HSCT recipients (SUPPRESS) randomised to receive prophylactic brincidofovir or placebo standard of care, failed to reach the primary end-point of reduction in CMV infection at week 24.[29] Diarrhoea was a significant adverse event; leading to difficulties in differentiating between gastrointestinal GVHD or brincidofovir-related diarrhoea.[29] Higher use of corticosteroids and greater frequency of GVHD were observed in the brincidofovir arm as well as a non-statistically significant increase in mortality (15.5% brincidofovir vs 10.1% placebo).[29] Evaluation of brincidofovir to prevent adenovirus infection in paediatric allogeneic HSCT has been terminated and there are no further plans for brincidofovir to be evaluated as an antiviral for other double stranded DNA viruses.

Adoptive CMV-specific T-cell therapy

Control of double stranded DNA herpes viruses that establish latency after initial infection is mediated by effective T-cell immunity. Thus, an obvious question has been whether it is possible to reinstate inadequate immunity after allogeneic HSCT using adoptive cellular therapy. This approach has been tested by multiple groups in the last two decades, modelling the positive outcomes demonstrated for EBV-specific T-cell therapy in EBV-driven post-transplant lymphoproliferative disease. In early phase clinical trials, CMV-specific T-cell therapy has proven to be effective in the treatment of active CMV tissue infection. While concerns have been raised about the potential negative effects of T-cell-mediated inflammatory responses in critically infected organs such as the lung, eye or brain, adverse clinical outcomes have not been a common finding.[30–32]

Indications for CMV-specific T cells include failure of prolonged or repeated cycles of treatment with ganciclovir and foscarnet or where these drugs cannot be administered due to toxicity. Generation of T cells may be performed using a donor venesection, leukapharesis or directly from the granulocyte-colony stimulating factor primed stem cell donation, where the product is specific for that donor's recipient.[33] Another option is to use CMV-specific T cells from third party donors that have been pre-generated and cryopreserved in banks for use at the time of CMV reactivation. In a recent study, 75% of allogeneic HSCT recipients showed improved viral load responses to CMV (and other viruses including EBV

and adenovirus) with partially human leukocyte antigen-matched virus-specific T cells.[32] Clinical benefits are long-lived despite the fact that persistence of the third party T cells at least in the blood is short term.[31] Donor-derived CMV-specific T-cell therapy in a prophylactic setting showed less frequent use and shortened duration of anti-CMV treatment.[30] Use of unmanipulated lymphocytes (donor lymphocyte infusion) from the original stem cell donor to treat CMV may be of benefit in a minority of cases but is frequently complicated by GVHD and has fallen out of favour in the era of antigen-specific T-cell therapy.

Within Australia, virus-specific T cells including CMV-specific T cells may be sourced from at least two academic institutions (Westmead Hospital Cell Therapies Group in Sydney and the Queensland Institute of Medical Research in Brisbane) and are currently being provided on compassionate grounds by Atara Biotherapeutics, a US-based biotechnology company. For patients with particularly high-risk disease such as those with pre-transplant CMV infection who will be undergoing T-cell depleted allogeneic transplantation (typically paediatric patients with immunodeficiency states), there may be sufficient time to plan and generate CMV-specific T cells from the stem cell donor for post-transplant use.

CMV vaccines and monoclonal antibodies

Immunisation against CMV could potentially reduce or prevent CMV disease. Results from a recent phase III HELIOS trial did not demonstrate improvement in overall survival or a reduction in CMV end-organ disease in CMV-seropositive HSCT recipients that received ASP0113, a bivalent DNA vaccine that encodes CMV glycoprotein B and phosphoprotein 65 antigens.[34] CSJ148 is a combination of two monoclonal antibodies (LJP538 and LJP539) directed against CMV glycoproteins that has been recently studied in preventing CMV disease in HSCT recipients.[35] Final study results are pending.

Conclusion

A better understanding of the impact of CMV on transplant outcomes, improvements in viral load and immune monitoring, development of new anti-CMV agents such as letermovir and maribavir together with emerging advances in viral-specific T-cell adoptive immunotherapy, will significantly impact on how clinicians will manage CMV in the future.

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