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Review Article

Update on Cytomegalovirus Infection Management in Allogeneic Hematopoietic Stem Cell Transplant Recipients. A Consensus Document of the Spanish Group for Hematopoietic Transplantation and Cell Therapy (GETH-TC)

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Abstract. ***Background*: Cytomegalovirus (CMV) infection is a common complication following allogeneic hematopoietic stem cell transplantation (allo-HSCT) and in patients receiving novel hematological therapies. Its impact on morbidity and mortality necessitates effective management strategies. Despite recent advances in diagnostics and treatment, unresolved questions persist regarding monitoring and treatment, prompting the need for updated recommendations.**
***Methods*: A consensus was reached among a panel of experts selected for their expertise in CMV research and clinical practice. Key clinical areas and questions were identified based on previous surveys and literature reviews. Recommendations were formulated through consensus and graded using established guidelines.**
***Results*: Recommendations were provided for virological monitoring, including the timing and frequency of CMV DNAemia surveillance, especially during letermovir (LMV) prophylaxis. We evaluated the role of CMV DNA load quantification in diagnosing CMV disease, particularly pneumonia and gastrointestinal involvement, along with the utility of specific CMV immune**

monitoring in identifying at-risk patients. Strategies for tailoring LMV prophylaxis, managing breakthrough DNAemia, and implementing secondary prophylaxis in refractory cases were outlined. Additionally, criteria for initiating early antiviral treatment based on viral load dynamics were discussed.

***Conclusion*: The consensus provides updated recommendations for managing CMV infection in hematological patients, focusing on unresolved issues in monitoring, prophylaxis, treatment, and resistance. These recommendations aim to guide clinical practice and improve outcomes in this high-risk population. Further research is warranted to validate these recommendations and address ongoing challenges in CMV management with emerging antiviral combinations, particularly in pediatric populations.**

Keywords: CMV; Antiviral prophylaxis; Preemptive antiviral therapy; CMV DNA doubling time; CMV-specific T-Cell immunity; Clinically significant CMV infection.

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Introduction. Active cytomegalovirus (CMV) infection occurs frequently after allogeneic hematopoietic stem cell transplantation (allo-HSCT) and is associated with increased morbidity and mortality.[1] Recently, CMV DNAemia and disease have also been observed in patients with hematological malignancies receiving molecular-targeting small molecules[2] and in recipients of chimeric antigen receptor T-cell therapy (CAR-T)[3,4] but their pathogenicity and clinical consequences remain to be determined. In the allo-HSCT setting, between 60 and 70% of CMV seropositive recipients (R) and between 20 and 30% of CMV seronegative patients transplanted with CMV seropositive donors (D) will develop CMV DNAemia after allo-HSCT in the absence of prophylaxis.[5] CMV may cause end-organ disease, increasing morbidity and mortality, which usually requires long-course antiviral treatment (at least 4 weeks) limited by common drug-related toxicities.[6] CMV-seropositive patients treated with allo-HSCT may exhibit deeper immunosuppression, which translates into lower overall survival compared to CMV seronegative patients, in particular for unrelated donors (URD) or D/R HLA mismatch1. This was also observed during the coronavirus disease (COVID-19) pandemic when CMV-seropositive recipients showed higher mortality than CMV-seronegative recipients.[7] In CMV seropositive patients, the risk of prolonged and/or recurrent reactivation, as well as mortality, is even higher when the donor is CMV-seronegative.[5,8] Recent years have seen advances in several areas, including the use of diagnostic tools, monitoring of specific anti-CMV T-cell immunity and molecular analyses of CMV mutations that translate into antiviral resistance, identification of risk factors and direct and indirect effects, and availability of new antiviral drugs for prophylaxis and/or treatment.[9] All these advances have prompted significant changes in the management and prophylactic strategies of this infection during the last five years in the transplant setting.[10] Many of these are included in current guidelines and recommendations,[11,12,13,14] although there are unanswered questions regarding the management/monitoring of CMV infection in daily clinical practice, including which groups of new hematological drugs need monitoring in treated patients, the frequency and duration of CMV monitoring, the utility of specific CMV T-cell monitoring, the significance of CMV DNAemia and/or CMV resistant features during letermovir (LMV) prophylaxis, and who could benefit from novel anti-CMV drugs and when. These issues were highlighted by a national survey conducted by the Infectious Complications Committee (GRUCINI) of the Spanish Group of Hematopoietic Transplantation and Cellular Therapy (GETH-TC).[15]

The objective of this consensus is to update recommendations and provide expert opinion on aspects not addressed by current guidelines or with low grade evidence.

Materials and Methods

Selection of experts and working method. For the preparation of this consensus, the GRUCINI-GETH-TC selected sixteen experts from among its members based on their expertise in CMV research and clinical practice. The Expert Panel included hematologists involved in transplant programs in adults (JLP, LV, RD, AP, CM, IE, MS-Ll, IG-C, RM, MR, RC, CS) or in pediatric patients (MG-V), hematologists involved in cell therapy production (MG) and virologists (EG, MAM, DN). The Expert Panel was assisted by a methodologist (AC) who was involved in the field of evidence-based medicine and guideline production as part of the GETH-TC secretary.

The Expert Panel agreed on key clinical areas and key questions within each clinical area, using the criterion of clinical uncertainty detected in the previous survey conducted by the GETH-TC in 21 centers, accounting for 71% of the allo-HSCT performed in Spain.[15,16] In addition, a specific survey was performed in Spanish transplant centers in 2022 on CMV DNAemia monitoring and management during LMV prophylaxis (see Summary Report, Supplementary material).

Specific questions were assigned to two experts and the methodologist, who conducted a literature search aimed at identifying trials and retrospective studies. Each group prepared a response proposal, which was reviewed by all the experts, and those reaching at least 90% consensus were accepted. A recommendation level was assigned using the grading system of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID)[17] (**Table 1, Supplementary material**). Those recommendations made by the group that are considered new or that have changed previous recommendations are highlighted in bold letters in the text.

Results

Virological Monitoring.

1. *Question 1: Should CMV DNAemia be monitored in hematological patients treated with CAR-T therapies, biologic therapies, or small-molecule therapies (BTK and JAK inhibitors) before or after allo-HSCT?*

CMV DNAemia is common (up to 45% in CMV-seropositive patients) in the CAR-T therapy setting within the first 90 days after infusion of CAR-T cells.[18,3,4] Although CMV DNAemia in these patients has been associated occasionally with end-organ CMV disease[19] and lower overall survival,[3,4] most episodes usually resolve without the need for antiviral treatment; however, CMV monitoring is suggested for high-risk patients (high-risk CAR-HEMATOTOX score) as well as those displaying CMV DNAemia before CAR-T infusion and those under corticosteroids therapy for cytokine release syndrome (CRS) or immune effector cell-associated neurotoxicity syndrome (ICANS),[20] starting at baseline and up to day 60 after CAR-T infusion (BIIu).

The JAK inhibitor, ruxolitinib, has received FDA and EMA approval as first-line treatment for steroid-refractory acute and chronic graft versus host disease (GVHD). Different studies have described CMV reactivation during ruxolitinib use in this setting.[21,22,23] However, given the strong association between acute GVHD and CMV reactivation,[24] only some studies have suggested that ruxolitinib treatment is a significant adverse prognostic factor for the complete response of first CMV reactivation. This was analyzed separately for each reactivation as a competing risk with death in a cause-specific Cox model of survival after the first GVHD occurrence, with the onset of ruxolitinib therapy coded as a time-dependent covariate.[23]

Therefore, the group considers that, at present, there is insufficient evidence to suggest the need to routinely monitor CMV DNA burden in patients treated with new therapies, including BTK inhibitors[25] and JAK inhibitors (BIIu).[26]

2. *Question 2: What is the optimal frequency and duration of monitoring in the allo-HSCT setting?*

Following recent guidelines, we recommend that all CMV allo-HSCT patients, regardless of donor and/or recipient CMV serostatus, should be monitored at least once a week starting in the first two weeks after infusion until day +100 post-allo-HSCT (AII).[11,12,13] After day +100, high-risk patients, including cord blood transplant (CBT) recipients, patients who start PET during the first 100 days, those who received extended letermovir prophylaxis beyond day +100, and those with moderate to severe acute or chronic graft-versus-host disease (GVHD) or treatment with high-dose corticosteroids, should be monitored with the same frequency until immunosuppression withdrawal (AII).[11,12]

Patients under LMV prophylaxis should be monitored following the same schedule as above (AI). Due to the mechanism of action of LMV, fragmented viral DNA can accumulate in the blood compartment in the absence of true CMV replication.[27,28] Current data support the idea that most episodes of CMV DNAemia occurring during LMV prophylaxis resolve without treatment, probably reflecting abortive CMV infections.[29,30] The most convenient CMV DNA threshold level or kinetics to guide pre-emptive antiviral therapy (PET) administration during CMV prophylaxis remains to be defined6. In the meantime, a relatively high threshold (i.e., 1,500 IU/mL in plasma; 10,000 IU/mL in whole blood) can safely be used to prompt PET inception (BII).

3. *Question 3: When should early treatment be started? It should be a high or low level of DNAemia / viral doubling time.*

The CMV loading threshold that determines PET initiation varies widely in transplant centers, typically between 1,000 and 10,000 IU/mL in whole blood or 100

to 1,500 IU/mL in plasma.[15] In most centers, the PET threshold is not adjusted to the patient's risk of CMV disease.[31] The CMV viral load threshold in blood to initiate PET should be established at each center, depending on the analytical characteristics of the qPCR and the matrix used. There is no clinical evidence, in terms of mortality incidence, that supports recommending the use of high or low thresholds for PET. Nevertheless, a recent systematic review of randomized and observational studies from 2013 to 2023 demonstrated that antiviral preemptive therapy started at CMV viral load thresholds between 2 and 3 log10 IU/mL was associated with similar CMV disease rates. Thus, viral thresholds in this range appear to effectively protect patients not receiving prophylaxis (BIIr).[32] Indeed, there is some evidence associating PET with higher mortality, suggesting that toxicity related with available anti-CMV drugs could be a matter of concern in this setting.[33]

Use of dt to start PET. Using the CMV DNA doubling time (dt) as a parameter for guiding PET is a recent suggestion. Using CMV load kinetics through the first two consecutive positive qPCR determinations to calculate the dt (spaced no more than 10 days apart and with load increments not less than 0.5 log10), it was determined that, in patients not receiving CMV prophylaxis, dt ≤2 days predicted the need to administer PET with a sensitivity of 100% when the established threshold for PET is 1,500 IU/mL (around 1,000 copies/mL).[34] This strategy results in shorter PET times, without a higher incidence of recurrent DNAemia.[35] The dt calculated from the CMV loads provided by different qPCRs is similar, given their collinearity for low load intervals, contrary to the magnitude of the loads.[36] The use of dt therefore allows direct comparison of results obtained in centers that use similar or different qPCRs. Therefore, the group recommends it dt use (BIII), in addition to qPCR CMV viral load, in the context of clinical trials, in order to generate evidence.

4. *Question 4: What is the value of CMV DNA load quantitation for diagnosing CMV disease, especially CMV pneumonia and gastrointestinal disease?*

Diagnosis of proven CMV pneumonia and gastrointestinal (GI) disease requires histopathological and virological evidence (observation of cytopathogenic effect/conventional culture/detection of viral proteins by immunohistochemistry -IHC- in biopsy material).[37] Detection of viral DNA in bronchoalveolar lavage (BAL) is not diagnostic, since it may simply reflect asymptomatic shedding.[37] The absence of CMV DNA in BAL has a negative predictive value close to 100%.[11,38,39] Although the probability of CMV pneumonia rises in parallel with increased viral load in BAL, especially in patients with a high pre-test probability, a diagnostic threshold has not been reached. A threshold value of 500 IU/mL has been suggested to discriminate between disease (higher values) and asymptomatic shedding (lower values).[38] In a subsequent study, it was confirmed that the presence of CMV loads greater than this threshold is frequent in the BAL of patients with a low probability of CMV pneumonia.[39] The lack of homogeneous BAL collection protocols and variability in the analytical characteristics of qPCRs make it extremely difficult to establish a universal diagnostic CMV burden threshold.

As in BAL samples, CMV DNA detection in feces or intestinal biopsies is not diagnostic. However, CMV-PCR shows the same sensitivity (100%), specificity (98%), and positive (93%) and negative predictive value (100%) as CMV-IHC in the G-I tract.[40] Nevertheless, the potential value of quantifying CMV load in intestinal biopsies requires further validation.

Immune Monitoring.

5. *Question 5: Specific CMV immune monitoring: in which patients and for what purpose?*

Systematic monitoring of the specific T-cell immune response against CMV could be useful to identify patients at risk for primary, recurrent or clinically refractory CMV DNAemia who are amenable to treatment with specific T lymphocyte-adoptive T cell transfer and end-organ disease.[41–43] The best marker of protection against these clinical events is the number of CD8+ and/or CD4+ T lymphocytes that express interferon gamma (IFNγ) after being stimulated in vitro with CMV antigens (particularly pp65 and IE-1).[41–43] Various protection thresholds have been proposed but not clinically validated. These cells can be quantified by flow cytometry with intracellular cytokine staining (ICS), ELISpot (CMV Tspot/CMV T-Track) or enzyme immunoassay (Quantiferon® CMV). The clinical value of quantifying specific T lymphocytes against CMV has been proven in a few non-randomized prospective intervention studies.[44,45] Systematic immunological monitoring of allo-HSCT patients is not currently standard practice, and this is unlikely to change until its clinical value is proven in randomized trials.[29] However, in particular cases (i.e., recipients with prior CMV DNAemia, those with GvHD and/or under corticosteroids, or after ending LMV prophylaxis), the lack of specific anti-CMV T cells could be used to support continuous CMV monitoring over time. The group therefore recommends monitoring CMV immunity whenever possible in order to generate real-world evidence.

CMV Infection Control Strategies.

6. *Question 6: Can we tailor the singular efficacy of LMV in CMV prophylaxis?*

Although end-organ CMV disease can generally be reduced with PET, CMV DNAemia itself has been

associated with increased non-relapse mortality in allo-HSCT receptors, suggesting deleterious indirect effects.[33] Several agents have been challenged as prophylaxis, but most did not demonstrate efficacy or were associated with an unacceptable toxicity.[46] Foscarnet (FOS) prophylaxis has been used in patients in uncontrolled trials only and its prolonged use as prophylaxis is limited by IV administration and toxicities.[47,48] Maribavir (MBV) failed to demonstrate a significant benefit on the incidence of DNAemia, CMV disease, or need of PET at week 24 and had no statistically significant effect in reducing mortality.[49] Finally, brincidofovir (BCDV) showed no significant difference in the incidence of clinically significant CMV infection (csCMV-I) at week 24 and was associated with increased GI toxicity.[50]

Only LMV reduced csCMV-I and all-cause mortality with a good safety profile.[51] Based on the results of the randomized phase 3 trial of letermovir prophylaxis, different guidelines have assigned it the highest level of recommendation (A-I).[11,12,13] Looking for patient subgroups that could most benefit, no significant differences were observed in the incidence of CMV DNAemia/pp65 antigenemia between the high-risk (related or unrelated donor with HLA mismatch, haploidentical donor, cord blood transplant, T-depletion, ATG or alemtuzumab use, GVHD grade ≥2) and low-risk groups (HLA-matched related or unrelated donor). A trend was observed towards higher incidence of CMV DNAemia in the haploidentical HSCT group, with no impact on mortality or CMV end-organ disease.[51] A meta-analysis published in 2018 confirmed LMV as the best option in terms of efficacy and safety.[52]

Single-center reports found that haploidentical HSCT with posttransplant cyclophosphamide (PTCy) resulted in either increased or comparable DNAemia incidence compared to historical comparisons of HLA-matched HCT.[53,54] In a recent retrospective registry-based study performed by the GETH-TC, multivariate analysis showed that the risk of DNAemia was significantly higher in haploidentical HSCT PTCy patients [HR (95%) 2.17 (1.52–3.10); p<0.001] and in unrelated donor HSCT patients [HR (95%) 1.49 (1.05–2.10); p<0.03] than when using an HLA-identical family donor16. Recently, however, PTCy itself (regardless of donor source or HLA match) has been considered a risk factor for DNAemia incidence.[55] In this study of the Center for International Blood and Marrow Transplantation Research (CIBMTR) comparing patients receiving haploHSCT with PTCy (n=757), matched related (MR) with PTCy (n=403), or MR with calcineurin inhibitor-based prophylaxis (CNI) (n=1605), cumulative incidences of DNAemia by day 180 were 42%, 37%, and 23%, respectively (P=0,001), without differences in end-organ CMV disease incidence.[55]

Based on this information (and only if universal prophylaxis with LMV is restricted), our recommendation would be to use LMV in higher-risk patients (BII), including: 1. Seropositive recipients allografted from seronegative CMV related or unrelated donor; 2. HSCT with at least one D/R HLA mismatch at the A, B or DR loci; 3. HSCT using PTCy; 4. CBT, and 5. Ex vivo T cell depletion.

7. *Question 7: When should LMV prophylaxis be withdrawn?*

Implementation of LMV in clinical practice has raised new questions, including those referring to the optimal duration. The pivotal trial observed a clear clinical benefit in all patients receiving LMV up to day +100 post-transplant, uniformly and independently of other characteristics and risk factors. However, it also showed a clear 12% increase in csCMV-I between discontinuation of LMV at day +100 and week 24. This increase in late events due to CMV after day +100 occurs preferentially in high-risk patients, particularly those with GVHD and on treatment with corticosteroids. These patients could potentially benefit from maintaining LMV prophylaxis beyond day +100.[51]

Recently, Russo et al. published the results of a phase III clinical trial to evaluate the efficacy and safety of LMV in prophylaxis maintained up to day +200 (NCT03930615).[56] After completing the first 100 days of prophylaxis, high-risk patients were randomized to continue receiving LMV versus placebo (ratio 2:1). The rate of csCMV-I between weeks 14 and 28 was reduced from 18.9% in the placebo group to 2.8% in the LMV arm (p<0.0005), with a safety profile and similar adverse effects in the two arms.[56] A 10% increase in csCMV-I has been also noted after LMV withdrawal, however, which warrants further CMV monitoring in high-risk patients after LMV stop.

Based on these results, we recommend continuing LMV prophylaxis until day +100 in all eligible patients, extended to at least until day +200 during active GVHD treated with corticosteroids (>0.5 mg/kg/day) (AI). In this setting, immunological monitoring could eventually prove useful to guide optimal duration of LMV prophylaxis (BII).

8. *Question 8: How should breakthrough DNAemia episodes during CMV prophylaxis be managed?*

A proportion of patients (7.4%) will present breakthrough DNAemia requiring PET while on prophylaxis with LMV[51] and risk factors been identified, including cumulative corticosteroid dose, PTCy use, and D-/R+ CMV serostatus.[57,58] As has been previously discussed, the most convenient CMV-DNAemia level to guide PET treatment initiation during LMV prophylaxis is not yet clearly defined. Nonetheless, our recommendation is to use a higher CMV DNAemia threshold than is used to guide PET in patients who do

not receive prophylaxis.[6] The group recommends not to treat a single positive PCR to avoid unnecessary antiviral therapy in self-resolving "blips" (the presence of CMV DNA at any level in a single plasma specimen, preceded and succeeded by a negative PCR specimen, 7 days apart)(BII).[59,60] In cases of breakthrough CMV DNAemia, we advocate performing molecular CMV mutational studies when possible. However, given that CMV DNAemia may be an expression of abortive infection due to the mechanism of action of letermovir, as discussed before, we and others recommend confirming active viral replication using virus isolation, DNAse technique, or by checking CMV-RNAemia before performing mutational studies.[61] Although the frequency of CMV mutations conferring resistance to LMV is low,[51] identifying UL56 gene mutations (V236M, C325W) may be helpful in avoiding extended LMV prophylaxis, switching to PET strategy and selecting the most adequate agent.[62]

9. *Question 9: Is secondary prophylaxis recommended in patients with recurrent CMV-DNAemia?*

A subset of patients will develop recurrent CMV-DNAemia, requiring several rounds of antiviral therapy. These patients are usually high (D-/R+), or high-intermediate (D+/R+) serological risk, receiving corticosteroids as GVHD treatment, and in the first six months post-HSCT.[59,60] In these cases, it would be clinically justified to perform secondary prophylaxis after CMV DNAemia clearance of the second episode of reactivation and maintain it until corticosteroids withdrawal or evidence of immune reconstitution.[29] As noted above, protective levels have been proposed but not yet clinically validated.[44]

Given the experience of real-life data of secondary prophylaxis,[63-66] LMV could be the treatment of choice in this situation, provided there is no LMV-resistant mutation and negative DNAemia before LMV onset (BII).[51,67–69] Secondary prophylaxis with LMV after initial failure of primary prophylaxis could be an option in cases of defective absorption suspicion in recipients with diarrhea, provided that CMV mutations conferring resistance to LMV can be reasonably excluded (BIII).

10. *Question 10: Is PET still an option as a primary strategy for CMV infection/disease?*

As mentioned above, the clinical superiority of prophylaxis with LMV over PET strategies has been demonstrated in phase III trial and several real-life studies. In countries where universal prophylaxis with LMV is not feasible, however, PET is the recommended strategy to prevent CMV disease, and the latter method is also used after LMV prophylaxis failure.

Intravenous ganciclovir (GCV) (AI) and oral valganciclovir (VGCV) are the most frequently used agents, with myelotoxicity and nephrotoxicity being the toxicity limitation.[11] A randomized clinical trial showed that FOS is as effective as GCV,[70] and therefore has the same recommendation level (AI). Since it presents less myelotoxicity than GCV, its use is recommended in patients with neutropenia or thrombocytopenia.

Recently a multicenter, double-blind, phase 3 study, patients with first asymptomatic CMV infection post-HCT compared maribavir 400 mg twice daily or valganciclovir for 8 weeks with 12 weeks of follow-up in 547 patients.[71] Although noninferiority of MBV to VGCV for the primary endpoint was not achieved based on the prespecified noninferiority margin, MBV demonstrated comparable CMV viremia clearance during post-treatment follow-up, with fewer discontinuations due to neutropenia. Although. MBV did not granted FDA/EMA indication as first line CMV PET, given its safety profile, the consensus recommend to considered it as an alternative in patients who develop neutropenia (BI).

11. *Question 11: When to stop antiviral therapy in PET strategies?*

ECIL and ASTCT guidelines recommend stopping PET upon negative PCR result after a minimum 15 days of treatment.[11,12] A recent small study suggests that PET can be stopped after the first negative PCR regardless of the duration of treatment up to that time point, without increasing the risk of recurrence and limiting drug-related toxicities as far as possible.[72] More studies are needed to change present guidelines, that the consensus support (AII).

Pharmacological Resistance.

12. *Question 12: When to suspect and how to confirm CMV resistance to antivirals?*

Definitions of CMV infection refractory (clinical) or resistant (genetic) to antivirals for use in clinical trials were proposed by Chemaly et al.[73] Nonetheless, the refractory definition should probably be wider in the clinical setting, including patients with long-lasting positive DNAemia of < 1 log or positive DNAemia after more than 21 days of PET onset.

Refractory CMV infection has a higher incidence than resistant in HSCT recipients, with rates varying between 29% to 39% and 1.7% to 14.5%, respectively.[74] This substantial difference is likely driven by poor host immunity in response to active viral replication, leading to refractory infection despite antiviral therapy and frequent underdiagnosis due to scarce diagnostic units for clinically useful time-results.[75]

Risk factors for the relatively common refractoriness and infrequent antiviral genetic resistance are summarized in **Table 2**, **Supplementary material**.[73]

Systematic studies in patients treated with allo-HSCT have shown an increasing incidence of genetic resistance, more frequently mutations in UL97 and much less

frequently in UL54.[76,77] The canonical mutations M460V/I, H520Q, C592G, A594V, L595S appear in 80% of cases and are associated with resistance only to GCV; therefore, diagnostic genotyping should include codon ranges of at least 440–640. Generally, mutations in the UL54 polymerase gene are preceded by mutations in the UL97 gene, increasing the level of resistance to GCV and conferring cross-resistance to FOS and cidofovir (CDV). This fact reinforces the importance of early virological study since the evolution of resistance and/or multi-resistance increases gradually and progressively with time of exposure to the antiviral drug.[78] For this reason, genetic resistance study is recommended when there is clinical suspicion.[11] Confirmation of resistance to antivirals is done by genotypic and phenotypic methods (see **Table 3**, **Supplementary material**).[79,80] In recent years, next generation sequencing (NGS) enabled the study of the entire spectrum of genetic diversity and can also detect mutations in virus populations of only 5%, which may play an important role in the evolution of virus resistance.[81,82] Based on these data, our recommendation is to perform mutational analysis if no negative DNAemia is achieved after three weeks of optimal antiviral treatment or if it increases after two weeks of treatment (BII).

13. *Question 13: How should refractory or resistant CMV infection be managed?*

Management of patients with refractory or genetically resistant CMV infection requires the use of an anti-CMV drug not resistant to the detected mutation, following the recommendations of the consensus group supported by ECIL-7 Guidelines.[11]

Until now initial treatment for a csCMV-I has usually been done with GCV or VGCV, and when refractoriness or (more commonly) severe pancytopenia appears, the drug of choice is FOS (AIIu) or CDV at 5 mg/kg/week if renal function is maintained (BIIu). Recently, oral MBV at a dose of 400 mg every 12 hours has been authorized and will be considered a new standard, at least in patients with hematological or renal toxicity (AI).[83] The combination of GCV and FOS at half doses can be used as second or third line (CIIu). Provided there is no clinical alloreactivity (active GVHD), immunosuppression should be reduced, including steroids (BIII). Leflunomide and artesunate can also be considered for third line treatment (CIII). Until now, there is no evidence that allows the use of LMV or BCDV as rescue treatments for refractory CMV infection.

Cell Therapy in CMV Infection.

14. *Question 14: When and in whom should adoptive transfer of virus-specific T lymphocytes be used?*

Adoptive transfer of virus-specific T cells (VSTs) has demonstrated safety and efficacy in treating virus-associated diseases and malignancies in HSCT, including CMV, adenovirus, BK virus, human herpesvirus,[6] and Epstein-Barr virus.[84] This has led to the recent approval of the first allogeneic anti-viral T cell product (tabelecleucel) for the treatment of EBV+ post-transplant lymphoproliferative disease.[85]

There are two main strategies for obtaining CMV-specific lymphocytes: direct magnetic selection using CMV tetramers/streptamers[86] or ex-vivo expansion of VSTs prior to infusion.[87] Both approaches have proven effective, but a direct comparison between them has not been made.

Currently, two phase III trials are employing adoptive cell therapy for CMV. In a prophylactic phase III study (EudraCT No. 2021-005105-27), posoleucel, a third-party multivirus-specific T cell therapy, was being evaluated for its potential to prevent CMV and other viral reactivations in high-risk HSCT patients, following promising results in the phase II trial.[88] However, the company (AlloVir) announced in December 2023 that they were discontinuing the phase III trial because pre-planned analyses showed it was unlikely to meet their primary endpoints. These results raise questions about the applicability of VSTs in the prophylactic context. In the treatment setting, the TRACE study (EudraCT No. 2018-000853-29) is a phase III trial testing a single infusion of allogeneic multi-specific VSTs generated using the CliniMACS Prodigy system and IFN-gamma magnetic capture for refractory viral infections after HSCT, including CMV. However, the trial is facing recruitment challenges, partly due to logistical complexities and time requirements for cellular product production. Nonetheless, this trial is anticipated to provide valuable insights into the treatment of CMV. An alternative approach, currently in development in academic centers and showing promise in phase 2 trials, involves establishing banks of third-party donor cryopreserved CMV-specific VSTs covering the most common HLAs. This ready-to-infuse off-the-shelf allogeneic therapy is expected to emerge as the cellular therapy solution for pharmacologically resistant/refractory CMV infection, with clinical trials warranted.

Concerning the clinical context of administration of CMV-CTLs, the consensus recommends to considered their use in the following patients (BII): a) with CMV organic disease resistant to first-line antiviral treatment; b) with resistant or refractory CMV DNAemia in two prior lines of treatment; c) with one or more documented genetic mutations associated with resistance to GCV or FOS, d) with recurrent (> 2 episodes) or persistent (> 6 weeks) CMV DNAemia, or e) with recurrent CMV-DNAemia with a low number of specific T lymphocytes against CMV identifying patients who are candidates for secondary prophylaxis or alternatively cell therapy.[29] By

contrast, the use of cell therapy is limited in patients receiving high dose corticosteroid (≥ 1 mg/Kg/day), ATG or alemtuzumab (DII).

15. *Question 15: Which antiviral drug combinations are available and/or under development?*

The availability of drugs with different mechanisms of action against CMV makes their combination attractive in refractory cases. Expert guidelines generally discourage the use of drug combinations, which are limited to GCV plus FOS suggested as second or third-line therapy with low levels of evidence.[11] However, various drug combinations active against CMV have recently been explored in in vitro models.[82] Studies of the in vitro effect of MBV showed additive interactions with FOS, CDV, LMV, and GW275175X in wild-type and mutant CMV strains, exhibiting great antagonism with GCV and strong synergy with sirolimus. In turn, LMV and sirolimus combined also showed an additive effect in vitro in terms of anti-CMV activity in epithelial cells. Although many combinations remain to be explored, these observations may be useful for designing future clinical studies in both prophylaxis and treatment.

The biological and clinical activity of the anti-CMV alternative agents is summarized in **Table 4**, **Supplementary material**.

16. *Question 16: Are there differences in CMV infection management in pediatric patients?*

Management of CMV infection is similar in pediatric and adult patients treated with HSCT, with the main differences deriving from the use of VGCV and LMV.

Valganciclovir. VGCV, a valine and GCV ester derivative, serves as an alternative to oral and intravenous administration for CMV prophylaxis and treatment. In adults, a daily dose of 900 mg provides GCV exposure equivalent to intravenous administration at 5 mg/kg. Limited data on VGCV use in children have been published, and no consensus on pediatric dosing has been established. Studies in pediatric transplant recipients emphasize the inadequacy of dosing algorithms based solely on body surface area, highlighting the importance of incorporating renal function, assessed by estimated creatinine clearance (CrCLS).[89] Age-independent bioavailability and predominant renal elimination of VGCV support the use of algorithms incorporating CrCLS in pediatric patients, achieving comparable GCV exposures to adults.[90] FDA approval for preventing CMV disease in high-risk pediatric transplant patients is based on a dosing algorithm with a maximum dose of 900 mg if CrCLS exceeds 150 mL/min/1.73 m². The requirement to take VGCV with food led to the development of an oral suspension (50 mg/mL), bioequivalent to tablets, benefiting pediatric patients unable to swallow.[91] The suspension is well-tolerated, with mostly mild or moderate gastrointestinal adverse events. A study on CMV mutations in pediatric patients using VGCV for prophylaxis indicated a low incidence of resistance-associated mutations, with no clinical consequences from resistant viruses.[92]

Letermovir. Recent results from a registry-based study of the Infectious Diseases Working Group of the Italian Association of Pediatric Hematology-Oncology (AIEOP),[93] a single center study[94] and the phase 2b open-label, single-arm clinical trial MK 8228-030 (NCT03940586)[95] have confirmed that pharmacokinetics, efficacy, safety, and tolerability of LMV in pediatric patients from birth to less than 18 years of age at risk of developing CMV infection and/or disease following HSCT are similar to adults. Administration of adult letermovir doses in this adolescent cohort resulted in exposures within adult clinical program margins and was associated with safety and efficacy similar to adults.[95]

Maribavir. In pediatric patients, a new clinical trial, SHP620-302: "A phase 3, multicenter, randomized, double-blind, double-dummy, active-controlled study to evaluate the efficacy and safety of MBV compared with VGCV for the treatment of CMV Infection in HSCT Recipients" to assess safety and effectiveness in children is ongoing.

Discussion and Summary of Recommendations. Advances in CMV monitoring and management have revolutionized approaches to infection control in transplant settings. From virological and immune monitoring to tailored prophylactic strategies and novel therapeutic interventions, ongoing research endeavors aim to optimize patient outcomes and mitigate the impact of CMV-related morbidity and mortality. Continued collaboration and multidisciplinary efforts are essential to address unanswered questions and refine existing guidelines, ultimately improving the standard of care for patients undergoing allo-HSCT. A summary of recommendations agreed by the consensus is detailed in **Table 1**.

This consensus highlights areas in need of further research to optimize CMV management. CMV DNAemia monitoring in patients undergoing CAR-T therapy remains contentious due to varying clinical outcomes and the potential for spontaneous resolution. In the allo-HSCT setting, the consensus recommends regular monitoring of CMV DNAemia in the patient when either the patient or donor is CMV seropositive, including those with GVHD or under letermovir prophylaxis. The emergence of CMV DNAemia during letermovir prophylaxis presents challenges in interpretation, with the ongoing debate surrounding the

Table 1. Consensus recommendations in key question topics.

Question Topic #	Recommendation
1. Monitoring CMV DNAemia in patients receiving CAR-T cell, biologic or small molecules before or after allo-HSCT:	Monitor CMV DNAemia before and until day 60 after CAR-T infusion or hematological toxicity recovery in high-risk patients. Routine monitoring is not necessary for patients treated with BTK inhibitors or JAK inhibitors unless clinically indicated.
2. Frequency and Duration of Monitoring in the allo-HSCT Setting:	Monitor patient at least once weekly post-allo-HSCT until day +100 when either the patient or donor is CMV seropositive. High-risk patients, including those with GVHD and/or extended corticosteroid treatment, should be monitored with the same frequency until immunosuppression withdrawal. LMV prophylaxis should be continued until at least day +100 and extended to day +200 during active GVHD treated with corticosteroids.
3. Initiation of PET Treatment:	Initiate PET based on CMV DNA load thresholds established at each center, considering CMV DNA doubling time ≤2 days as a parameter for guiding PET, particularly when the viral load threshold is set at 1,500 IU/mL.
4. Value of CMV DNA Load Quantitation in Diagnosis:	CMV DNA load quantitation alone is not diagnostic for CMV pneumonia or gastrointestinal disease. Other diagnostic methods such as histopathological and virological evidence are required.
5. Immune monitoring:	Systematic immunological monitoring of allo-HSCT patients is not currently standard practice. However, the group recommends monitoring CMV immunity whenever possible in order to generate real-world evidence.
6. Tailoring LMV Prophylaxis:	LMV prophylaxis is recommended in all CMV seropositive allo-HSCT recipients. If universal prophylaxis is restricted, LMV is highly recommended as the first-line option in high-risk patients, including those with seropositive recipients allografted from seronegative CMV donors, HSCT with at least one D/R HLA mismatch, haploidentical HSCT, and HSCT using PTCy.
7. Withdrawal of LMV Prophylaxis:	Continue LMV prophylaxis until at least day +100 in all candidate patients and extend it to day +200 during active GVHD treated with corticosteroids (>0.5 mg/kg/day). Immunological monitoring could eventually guide the optimal duration of LMV prophylaxis.
8. Management of Breakthrough DNAemia During CMV Prophylaxis:	Use a higher CMV DNAemia threshold for initiating PET during LMV prophylaxis. Consider molecular CMV mutational studies in cases of breakthrough DNAemia to guide treatment decisions.
9. Secondary Prophylaxis in Patients with Recurrent CMV-DNAemia:	Consider secondary prophylaxis with LMV in patients with recurrent CMV-DNAemia, particularly after clearance of the second episode of reactivation, until corticosteroids withdrawal or evidence of immune reconstitution.
10. Use of PET as a Primary Strategy for CMV Infection/Disease:	PET is recommended as a primary strategy for CMV infection/disease prevention in settings where universal prophylaxis with LMV is not feasible, and after LMV prophylaxis failure.
11. Duration of Antiviral Therapy in the PET Strategy:	Consider stopping PET after the first negative PCR, without increasing the risk of recurrence, to minimize drug-related toxicities.
12. Suspicion and Confirmation of CMV Resistance:	Perform mutational analysis if no negative DNAemia is achieved after 3 weeks of optimal antiviral treatment or an increase occurs after 2 weeks of treatment. Utilize genotypic and phenotypic methods for confirmation of resistance to antivirals.

Question Topic #	Recommendation
13. Treatment of Refractory or Resistant CMV Infection:	Use anti-CMV drugs not resistant to detected mutations. Consider oral MBV as a new standard, especially in patients with hematological or renal toxicity. Reduce immunosuppression and consider combination therapy based on clinical scenarios.
14. Use of Cell Therapy:	Consider adoptive transfer of virus-specific T lymphocytes (VSTs) in various clinical scenarios, including refractory CMV infection. Explore ongoing clinical trials evaluating the efficacy of adoptive cell therapy.
15. Alternative Drugs and Combinations:	Investigate potential antiviral drug combinations for refractory CMV infection, guided by in vitro studies.
16. Management of Pediatric Patients:	Tailor management approaches in pediatric patients, considering challenges in dosing algorithms and ongoing clinical trials evaluating drug efficacy and safety.

need and threshold for PET inception. The utilization of CMV DNA doubling time (DT) has emerged as a promising tool to guide PET initiation, ensuring timely intervention without compromising patient outcomes.

Assessment of CMV-specific T-cell immunity might identify patients at risk of CMV DNAemia and help guide therapeutic interventions. While systematic immunological monitoring is not yet standard practice, it may be warranted in specific clinical scenarios, such as recipients with prior CMV DNAemia or those with GVHD. Further research is needed to validate the clinical utility of immune monitoring and establish standardized protocols.

LMV has emerged as a cornerstone in CMV prophylaxis, demonstrating efficacy and safety in reducing CMV infection and mortality post-HSCT. Nonetheless, personalized prophylactic strategies can be informed by identifying risk factors such as the use of posttransplant cyclophosphamide, the real significance of breakthrough DNAemia, and the use of CMV-specific T-cell immunological monitoring. Careful consideration of antiviral drug selection is essential in cases of breakthrough CMV DNAemia during prophylaxis, with emphasis on avoiding unnecessary toxicity and assessing for potential LMV resistance mutations. Furthermore, implementing secondary prophylaxis with LMV may be warranted in patients with recurrent CMV DNAemia, provided that careful monitoring for resistance mutations is also carried out.

The emergence of CMV resistance to antiviral therapy poses challenges in clinical management, underscoring the importance of promptly identifying and selecting alternative agents. Mutational analysis is recommended for cases of refractory CMV infection. However, in this context, antiviral pharmacological combinations lack support from clinical trials, and access to adoptive transfer of virus-specific T lymphocytes is limited in most centers. Currently, available data are derived from heterogeneous studies conducted in different clinical contexts; therefore, optimal dosing and administration schedules for VSTs are not known. Nonetheless, clinical responses have been achieved even with doses as low as 4.1 x 103/kg.[96] It should also be taken into account that efficacy partly depends on in vivo expansion and that memory cells have a greater potential for expansion than terminally differentiated T cells;[97] therefore, selecting this subset may improve the efficiency of the product. To date, most trials exploring the use of adoptively transferred viral-specific T cells have been in second or later lines of therapy after the failure of antiviral drugs.

Despite issues of feasibility and the potential for failure due to viral recognition through a non-shared HLA allele in the HLA-disparate setting, HSCT donor-derived viral-specific T cells have demonstrated benefit for refractory infections as well as for prophylaxis and first-line treatment. Infusion of third-party derived partially HLA-matched VSTs has a demonstrated benefit in the refractory setting but could be considered as a first-line therapy or even prophylactically in high-risk patients with predicted intolerance to antiviral medications due to organ dysfunction. The preliminary feasibility, safety, and efficacy of allogeneic, off-the-shelf, multi-virus-specific T-cell therapy has been demonstrated for use as first-line therapy[98] and as prophylaxis.[99] As a next step, further research is needed to elucidate optimal treatment strategies and mitigate the risk of resistance development.

In pediatric patients, valganciclovir and letermovir are promising options for CMV prophylaxis and treatment, with ongoing studies evaluating safety and efficacy. Pediatric-specific dosing algorithms and clinical trials are essential to ensure optimized management strategies tailored to this patient population.

Author's Contribution. Each author identified, reviewed, and summarized the literature and their own experience on the assigned key questions and approved the final version of the manuscript. CS, JLP, and DN drafted the manuscript.

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