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REVIEW ARTICLE

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Assessment and prevention of cytomegalovirus infection in allogeneic hematopoietic stem cell transplant and in solid organ transplant: A multidisciplinary consensus conference by the Italian GITMO, SITO, and AMCLI societies

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Abstract

Cytomegalovirus (CMV) remains a major cause of morbidity and mortality in allogeneic hematopoietic stem cell transplantation (allo-HSCT) and solid organ transplantation (SOT) recipients. In view of the uncertainties on the assessment and prevention of CMV infection in both transplant procedures, three Italian scientific societies for HSCT and SOT and for Clinical Microbiology appointed a panel of experts to compose a framework of recommendations. Recommendations were derived from a comprehensive analysis of the scientific literature and from a multidisciplinary consensus conference process. The lack of adequate clinical trials focused on certain

diagnostic procedures, and antiviral intervention forced the panel to use the methods of consensus for shaping some recommendations. Recommendations concerning the two types of transplant were given for the following issues: assessment of pretransplant CMV serostatus, immunological monitoring after transplant, CMV prophylaxis with antivirals, CMV preemptive strategy, and CMV prophylaxis with immunoglobulin infusion and with adoptive immunotherapy. The questions raised by and the recommendations resulting from this consensus conference project may contribute to the improvement of certain crucial aspects of the management of CMV infections in allo-HSCT and in SOT populations.

KEYWORDS
cytomegalovirus, diagnosis, hematopoietic stem cell transplant, preemptive therapy, prophylaxis, solid organ transplant

1 | INTRODUCTION

Human cytomegalovirus (CMV) remains a major cause of morbidity and mortality in allogeneic hematopoietic stem cell transplantation (allo-HSCT) and solid organ transplantation (SOT) recipients.[1] CMV infection is associated with increased post-transplant complications, such as poor-graft function, graft failure, and chronic graft-vs-host disease (GVHD) in allo-HSCT, allograft dysfunction, acute and chronic graft rejection in SOT, and other opportunistic infections in both transplants.[1,2]

Several diagnostic and therapeutic issues remain critical, and the uncertainties on assessment and prevention of CMV infection represent unmet clinical needs and risks of harm for both allo-HSCT and SOT patients.

Moving from these considerations, three Italian scientific societies for HSCT (Gruppo Italiano Trapianto di Midollo Osseo, GITMO), SOT (Società Italiana di Trapianto d'Organo, SITO), and Clinical Microbiology (Associazione Microbiologi Clinici Italiani, AMCLI) appointed a panel of experts to produce recommendations on the assessment and prevention of CMV infection in allo-HSCT and in SOT recipients.

2 | DESIGN AND METHODS

Two chairmen (CG and GB) appointed an expert panel (EP) of other 14 members, selected from who had previously published and/or expressed an interest in CMV infection in transplant. During an initial meeting, the EP examined the current state of knowledge on the area of interest and agreed on the issues of major concern in the risk of CMV infection during transplant by defining clinical key questions using the criterion of clinical relevance through a Delphi process. The following five issues formed the set of key questions of the present consensus project: "assessment of pre-transplant serological CMV status and specific CMV immunological monitoring before and after transplant," "antiviral prophylaxis strategy," "pre-emptive strategy," "prophylaxis with immunoglobulin infusion," and "prophylaxis with adoptive immunotherapy."

During two consensus conferences held in Milan, Italy, each panelist first drafted statements that addressed one or more of the preliminarily identified key questions, then scored her/his agreement with the statements made by other panelists, and provided suggestions for rephrasing. The overall goals of the meetings were to reach a consensus over question-specific statements for which there was disagreement during the first-round postal phase. Participants first commented on their preliminary votes in round-robin fashion and then a new vote was proposed until at least 80% consensus on the statement was achieved. If an 80% consensus was still not attained, the issue was declared undecidable, and no further attempt was made. The quality of evidence and strength of recommendation were graded according to the IDSA grading system (Table 1).[3]

TABLE 1 Quality of evidence and strength of recommendations: IDSA grading system

Quality of evidence	Strength of recommendation
I: Evidence from at least one properly randomized controlled trial	A: Good evidence to support a recommendation for or against use
II: Evidence from at least one well-designed clinical trial without randomization; from cohort or case-controlled analytic studies (preferably from more than one center); from multiple time-series studies; or from dramatic results from uncontrolled experiments	B: Moderate evidence to support a recommendation for or against use
III: Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports from expert committees	C: Poor evidence to support a recommendation

3 | RESULTS

3.1 | What is the appropriate assessment of pretransplant CMV status and specific immunological monitoring before and after transplant?

3.1.1 | Allo-HSCT recipients

In allo-HSCT, CMV-seronegative recipients (R-neg) receiving transplant from a CMV-seronegative donor (D-neg) are at the lowest risk of CMV reactivation and disease while R-pos receiving transplant from a D-neg are at the highest risk.[1] CMV serostatus may significantly impact on the transplant-related mortality, although in allo-HSCT type of hematologic disease, intensity of conditioning, type of transplant, and type of donor are variables which may modulate the impact of donor CMV serological status on the patient outcome. The prognostic impact of donor and recipient CMV serostatus was evaluated in recent analyses from the database of the European Blood and Marrow Transplantation (EBMT) group.[4-7] In acute leukemia patients, transplants with D-pos and/or R-pos were associated with a significantly decreased 2-year leukemia-free survival (LFS) and overall survival (OS), and increased non-relapse mortality (NRM) compared with R-neg who underwent transplant from a D-neg.[4] In another analysis, R-neg receiving transplant from unrelated D-pos had decreased OS compared with unrelated D-neg, but no difference was observed when the D-neg was a HLA-identical sibling.[5] In the same study, R-pos receiving grafts from unrelated D-pos demonstrated improved OS compared with D-neg only in the setting of myeloablative conditioning. In acute leukemia R-pos submitted to non–T-cell-depleted haploidentical HSCT with post-transplant cyclophosphamide, the 1-year NRM and OS of the D-pos/R-pos and D-neg/R-pos pairs were comparable.[6] The prognostic impact of the donor/recipient CMV serostatus was also evaluated in patients with chronic hematologic malignancies. Transplants with D-pos and/or R-pos were associated with a significantly reduced 2-year progression-free survival, OS, and NRM. Worst OS was observed in the couple R-pos/D-neg, followed by the couple R-pos/D-pos. Conversely, OS did not differ significantly between R-pos/D-pos and R-neg/D-neg transplants.[7]

The CMV-specific T-cell response is an important predictor of post-transplant CMV infection/disease. A variety of methods to measure cell-mediated immunity (CMI) response are available.[8] Most of the experience regarded interferon-gamma releasing assays (IGRAs) which detect and quantify T-cell responses following antigen-specific stimulation. QuantiFERON-CMV is the only IGRA approved for clinical use for CMV immune monitoring. In this test, whole blood is stimulated with CMV peptides and IFN-γ released from CMV-specific CD8+ T cells is quantified by an immunoenzymatic test. Another IGRA is the CMV ELISpost (enzyme-linked immunospot) assay which is able to detect and quantitate response of both CD4+ and CD8+ T cells.

In allo-HSCT, CMI tests should be performed after engraftment. In this population, there is no rationale to test CMI before transplantation and after transplantation before engraftment when recipients are lymphopenic. The minimal number of CD3+ T cells required for robust results has not been established yet, although some laboratories have established the minimum cut-off of 100 T lymphocytes/cmm. Numerous studies have assessed CMI assays to determine the risk of CMV infection/disease after allo-HSCT (Table 2).[9-14] IGRAs were performed weekly or monthly after engraftment until 100 days or 12 months from transplant.[9-14] CMV-specific immunity reconstitution was variably associated with lower incidence of CMV infection/disease, lower rate of CMV infection recurrence, higher spontaneous viral clearance, and lower peak viral loads. These experiences suggest that the results of CMI tests may be considered to guide the use of antiviral drugs in terms of duration of prophylaxis and decision to start or define the length of antiviral therapy.

Recommendations

- In both donor and recipient of allo-HSCT, anti-CMV IgG should be evaluated before transplant (A II). Serologic tests with high sensitivity and high specificity are recommended. A test measuring CMV-specific IgG should be used, as serologic tests measuring IgM or IgG and IgM combined have poorer specificity and may cause false-positive results. When the donor or recipient is seronegative during the pretransplant, evaluation serology should be repeated at the time of transplantation (BIII).
- If the recipient is seronegative, a seronegative donor should be searched and possibly selected particularly in transplants from HLA-mismatched donors (AII).
- The donor workup should include anti-CMV IgM (BIII). Anti-CMV IgM-positive candidate donors should be temporarily excluded from donation while waiting for CMV DNAemia (BIII).
- In allo-HSCT, CMI monitoring is recommended after engraftment and should be repeated monthly until 3-12 months from transplant based on the viral infection risk of the patient and/or in the event of CMV reactivation (BII). Virus-specific T-cell responses measurement is no more required when CMV-specific CMI is detected (BII). In these cases, antiviral prophylaxis could be discontinued (BII) and the strategy of waiting for a spontaneous viral clearance without treatment or using a shorter viral treatment may be considered (BII). Conversely, patients with a poor CMV-specific T-cell response may be candidate to an intensive viral monitoring and aggressive/prolonged antiviral prophylaxis or therapy (BII).

3.1.2 | SOT recipients

Also in SOT, R-neg receiving transplant from a D-neg are at the lowest risk of CMV infection. Contrary to allo-HSCT, CMV "D-pos-R-neg" mismatch constitutes the highest risk scenario for CMV infection/disease after SOT.[1] Interpretation of serology results can be difficult in donors and recipients with recent transfusion of intravenous immunoglobulins and other blood products (platelets,

TABLE 2 Results of studies on CMV-specific cell-mediated immunity (CMI) assessment in SOT and HSCT recipients published in the last 5 years

Author, year (reference)	Type of transplant population (no. of patients)	Design of study	Results	Authors' comment
Navarro et al, 2016 [9]	Allo-HSCT (61)	Prospective, multicenter, matched comparison-group study to evaluate the efficacy and safety of a novel strategy that consisted of interrupting anti-CMV therapy upon CMV DNAemia clearance and concurrent detection of specific interferon-γ-producing CD8+ T cells (within 30 d after the initiation of therapy). Immunological monitoring was performed on days +7, +14, +21, and +28 after treatment initiation	56 patients were included in the matched-control group. Eleven patients (18%) fulfilled the criteria for antiviral treatment interruption. The cumulative incidence of recurrent CMV DNAemia was significantly lower (P = .02) in these patients than in patients in the comparative groups. Likewise, the length of antiviral treatment courses was significantly shorter in these patients than that in patients in the matched-control group (P = .003)	These data support the clinical utility of combining immunological and virological monitoring for the management of CMV infection and antiviral treatment duration in a subset of HSCT recipients
Bono et al, 2016 [10]	Allo-HSCT (22)	In the first 100 d after transplant, patients were monitored weekly for CMV DNAemia and twice a month for QT-CMV. Then, both tests were conducted once a month for a year	All seropositive patients had CMV first reactivation 10-48 d after transplant, but none of seronegative patients. 10 patients acquired specific CMV immunity 27-180 d after transplant, and 6 always remained QT-CMV-negative. Patients with CMV-specific immunity cleared spontaneously 67% of DNAemia episodes, while the same happened to only 15% of QT-CMV-negative patients also in need of a longer period of antiviral therapy	QT-CMV emerges as an easy tool to introduce immunological methods in the post-transplant monitoring of HSCT patients. CMI response frequently predicts spontaneous CMV DNAemia clearance
Nesher et al, 2016 [11]	Allo-HSCT (63)	CMV-seropositive recipients were prospectively evaluated with CMV ELISpot and for CMV infection from the period before transplantation to day 100 after transplantation	Based on the multivariable Cox proportional hazards regression model, the only significant factor for preventing CMV reactivation was a CMV ELISpot response. Positive assay identified patients who were protected against CMV infection as long as they had no GVHD and/or were not receiving systemic corticosteroids	Use of CMV ELISpot may reduce the duration and intensity of CMV monitoring and the duration of prophylaxis or treatment with antiviral agents in those who have achieved CMV-specific immune reconstitution
Yong et al, 2017 [12]	Allo-HSCT (94)	In an observational, multicenter, prospective study, CMV-specific T-cell immunity at baseline, 3, 6, 9, and 12 mo after transplant was evaluated using the QT-CMV, CMV ELISpot, and intracellular cytokine staining	At 3 mo after allo-HSCT, participants who developed CMV disease (n = 8) compared with CMV reactivation (n = 26) or spontaneous viral control (n = 25) had significantly lower CD8+ T-cell production of interferon-γ (IFN-γ) in response to CMV antigens measured by QT-CMV (P = .0008). An indeterminate QT-CMV result had a positive predictive value of 83% and a negative predictive value of 98% for identifying participants at risk of further CMV reactivation	Quantifying CMV-specific T-cell immunity after HSCT can identify participants at increased risk of clinically relevant CMV-related outcomes
Paouri et al, 2018 [13]	Allo-HSCT pediatric (37)	CMV DNAemia was detected via weekly real-time PCR. The QT-CMV test was conducted pretransplant, early after transplantation, 30, 90, 180, 270, and 360 d post-transplantation	The incidence of CMV viremia was 51% (19/37) with half of the episodes within ≤30 d post-transplant. 15 patients showed CMV-specific immunity (average of 82 d). The cumulative incidence of CMV reactivation in patients who developed CMV-specific immunity was lower than those who did not (15% vs 53%; P = .023)	QT-CMV was a valuable method for identifying pediatric HSCT patients at high risk of CMV DNAemia, suggesting potential clinical utility to individualize patient's management post-transplant

(Continues)

TABLE 2 (Continued)

Author, year (reference)	Type of transplant population (no. of patients)	Design of study	Results	Authors' comment
Krawczyk et al, 2018 [14]	Allo-HSCT (34)	CMV-specific CMI responses were monitored by QT-CMV test for a period of 12 mo after transplantation in 9 high-risk (D−/R+), 14 intermediate-risk (D+/R+), and 3 low-risk individuals (D+/R−), and 8 CMV-negative controls (D−/R−)	CMV reactivation was detected in all high-risk and 13/14 intermediate-risk individuals during the first 3 mo from transplant. Reconstitution of the CMV-specific CMI response was detected from 3 mo after transplantation and resulted in protection against CMV reactivation. CMI response was more pronounced in the D-pos/R-pos group as compared to de D-neg/R-pos group. A QT-CMV threshold of 8.9 IU/mL correlated with protection from high-level DNAemia	Monitoring of allo-HSCT recipients with the QT-CMV assay might be of great benefit to optimize antiviral treatment
Lucia et al, 2014 [18]	Kidney transplant (129)	The presence of pretransplant CMV-specific memory B and T cells by CMV ELISpot and clinical outcome in kidney transplant recipients between 43 R− and 86 R+ patients was compared	All R+ patients showed a wide range of CMV-specific memory T- and B-cell responses. High memory T- and B-cell frequencies were also clearly detected in 30% of R− patients, and those with high CMV-specific T-cell frequencies had a significantly lower incidence of late CMV infection after prophylactic therapy. ROC curve analysis for predicting CMV viremia and disease showed a high area under the ROC curve (>0.8), which translated into a high sensitivity and negative predictive value of the test	Assessment of CMV-specific memory T- and B-cell responses by CMV ELISpot before kidney transplantation among R− recipients may help identify immunized individuals more precisely, being ultimately at lower risk of CMV infection
Costa et al, 2014 [19]	Kidney transplant (328)	Patients were studied by CMV ELISpot: 201 prospectively monitored in the first year post-transplantation, 127 with a single determination at >1 y. Clinical features, including occurrence of CMV DNAemia, CMV serostatus, antiviral strategies, and immunosuppressive protocols, were evaluated	66.5% of patients were CMV responders at CMV ELISpot. No episode of infection occurred at follow-up (mean: 24.5 mo) in 73.4% responders vs 55.5% nonresponders ($P < .005$); CMV-free period was significantly longer in responders ($P < .001$). Although no significant difference in peak viral load was found, prevalence of CMV DNAemia values >105 copies/mL was significantly higher in nonresponders vs responders (8.2% and 2.3%, $P < .05$). Nonresponder status was significantly associated with CMV seronegativity ($P < .0001$), antiviral prophylaxis use ($P < .0001$), and immunosuppression induction with basiliximab ($P < .005$)	Immunological data for CMV could be used in the clinical evaluation and decision-making process, in combination with virological monitoring, in kidney transplant recipients
Rittà et al, 2015 [20]	Kidney transplant (80)	The impact of pretransplant CMV-specific host cellular immunity on the long-term risk of CMV replication in transplants was prospectively evaluated by CMV ELISpot.	At pretransplantation, 49 patients (61.3%) were responders by CMV ELISpot. At 3-month follow-up, 16 (32.7%) out of 49 CMV responders showed CMV blood infection, compared with 8 (25.8%) out of 31 nonresponders. No further episode of CMV viremia was reported in the responder group, in comparison with 15 out 31 nonresponders (48.4%) showing at least one episode of CMV DNAemia at 12-month follow-up. Recipients exhibiting at least one episode of CMV viremia at 12-mo follow-up showed lower baseline CMV ELISpot values than those without signs of CMV replication	This study suggests that monitoring CMV-specific T-cell responses at pretransplantation by CMV ELISpot assay may be useful for predicting the post-transplantation risk of CMV infection and reactivation

(Continues)

TABLE 2 (Continued)

Author, year (reference)	Type of transplant population (no. of patients)	Design of study	Results	Authors' comment
Kim et al, 2015 [21]	Kidney transplant (69)	Patients underwent CMV pp65 and IE1-specific CMV ELISpot assays before transplantation. CMV infection was defined in the presence of CMV antigenemia, CMV syndrome, or tissue-invasive CMV disease	Of the 69 patients, 27 (39%) developed CMV infections. There was no association between the IE1-specific CMV ELISpot and CMV infection. However, only 15 (31%) of the 48 patients with positive pp65-specific CMV ELISpot results (>10 spots/2.0 × 105 cells) developed CMV infections, whereas 12 (57%) of the 21 patients with negative pp65-specific CMV ELISpot results developed CMV infection (P = .04)	Negative pp65-specific CMV ELISpot assay results before transplantation appear to predict the subsequent development of CMV infections after transplantation in CMV IgG+ recipients
Kumar et al, 2017 [22]	SOT (overall, 27; kidney n. 7; liver, n. 10; lung, n. 6; and combined n. 4)	Transplant patients were enrolled at the onset of CMV viremia requiring antiviral therapy. CD8 T-cell responses were determined using the QT-CMV, and results were used to guide subsequent management	A total of 27 patients were treated until viral load negative. At end of treatment, 14/27 (51.9%) had a positive CMV response and had antivirals discontinued. The remaining 13/27 (48.1%) patients had a negative CMV response and received 2 mo of secondary antiviral prophylaxis. In those with a positive CMI and early discontinuation of antivirals, only a single patient experienced a low-level asymptomatic recurrence. In contrast, recurrence was observed in 69.2% of negative CMI patients despite more prolonged antivirals (P = .001)	This study demonstrated the feasibility and safety of real-time CMV-specific CMI assessment to guide changes to the management of CMV infection
Lee et al, 2017 [23]	Kidney transplant (124)	The aim of this study was to evaluate QT-CMV and CMV ELISpot (against CMV pp65 and IE-1 antigens) during early post-transplant period as a predictor of the development of CMV infection in CMV-seropositive patients	CMV DNAemia occurred in 16 (12.9%) patients within 3 mo after transplant. Post-transplant pp65 or IE-1 CMV ELISpot response, but not QT-CMV, was significantly associated with CMV DNAemia. The pp65 CMV ELISpot and IE-1 CMV ELISpot at post-transplant 1 mo predicted the risk of post-transplant CMV DNAemia (P = .019). Negative predictive values for protection from CMV DNAemia in case of positive ELISPOT results were 94.5% and 97.6% in pp65-ELISPOT and IE-1- CMV ELISpot assays, respectively	These results suggest that the variability may exist between CMV ELISpot assays and QT-CMV, and CMV ELISpot at post-transplant 1 mo can identify the risk of CMV DNAemia in seropositive kidney transplant recipients
Schachtner et al, 2017 [24]	Kidney transplant (326)	Patients were studied and classified with respect to CMV serostatus and the presence of CMV-specific T cells. Samples were collected pretransplantation, at +1, +2, and +3 mo post-transplantation. CMV-specific T cells directed to CMV-IE1 and CMV-pp65 were measured by CMV ELISpot	19 (28%) of 67 D + R− transplants showed pretransplant CMV-specific T cells. Although no differences were observed for CMV replication, transplants with CMV-specific T cells presented with lower initial and peak CMV loads (P < .05). Transplants with decreasing/undetectable CMV-IE1-specific T cells pretransplantation and post-transplantation were at greatest risk of CMV replication. KTRs with stable/increasing CMV-IE1-specific T cells from pretransplantation to post-transplantation, however, showed low risk of CMV replication (P < .001). One hundred sixty-two (80%) of 203 R+ transplants showed pretransplant CMV-specific T cells. Decreasing/undetectable CMV-IE1-specific T cells from pretransplantation and post-transplantation identified those R+ transplants at increased risk of CMV replication (65/80 transplants; 81%; P < .001)	Despite CMV prophylaxis, D + R− transplants are at greatest risk of CMV disease. Our data suggest that monitoring CMV-specific T-cell kinetics from pre-transplantation to post-transplantation, particularly directed to CMV-IE1, offers superior risk stratification compared with CMV serostatus alone

(Continues)

TABLE 2 (Continued)

Author, year (reference)	Type of transplant population (no. of patients)	Design of study	Results	Authors' comment
De Gracia-Guindo et al, 2018 [25]	Kidney transplant (75)	The clinical utility of QT-CMV just before transplant to predict CMV infection and if reactive result in QT-CMV could be predictor of the duration of treatment were evaluated	50% of patients had CMV infection, and 35.9% had CMV disease. The probability of CMV infection was lower with positive QT-CMV (P = .025)	IFN-gamma response measured by QT-CMV is a protective factor against CMV infection in post-transplantation kidney recipients
Gliga et al, 2018 [26]	Kidney transplant (30)	Patients were stratified according to their CMV IgG status pretransplantation [and were divided into two groups: preemptive (donor-/recipient+, donor+/recipient+) and prophylaxis (donor+/recipient−)]. A CMV ELISpot was performed at month 1 post-Tx (preemptive group) and end of prophylaxis and 1 mo thereafter (prophylaxis group). QT-CMV was performed every 2-4 wk (preemptive) or monthly (prophylaxis), in parallel to the CMV DNAemia load	A good positive agreement was obtained between the QT-CMV or CMV ELISpot and the CMV IgG. A cutoff of 19.5 spot forming units (SFU)/200 000 lymphocytes for the CMV ELISpot IE-1 (AUC = 0.802, sensitivity 45%, specificity 100%) and 495 SFU/200 000 lymphocytes for the CMV ELISpot pp65 (AUC = 0.617, sensitivity: 11%, specificity: 100%) was defined to assess protection against reactivation. The QT-CMV performed modestly (AUC = 0.477, cutoff 85.1 IU/mL)	The QT-CMV and CMV ELISpot enable the functional assessment of CMV-specific CMI in transplant recipients. In combination with CMV viral load monitoring, CMV ELISpot results could stratify patients at risk of CMV reactivation/infection
Chiereghin et al 2018 [27]	Heart transplant (44)	CMV-seropositive patients were enrolled: 17 received antiviral prophylaxis, and 27 were managed preemptively. QT-CMV was retrospectively performed on blood samples collected at five post-transplant time points	Higher proportion of patients with an indeterminate QT-CMV result after the suspension of prophylaxis than of patients who showed a global T-cell responsiveness developed CMV infection (P = .036). Patients who reconstituted a CMV-specific response following the first CMV DNAemia-positive result (42.9%) showed a median CMV DNAemia peak 1 log of magnitude lower than that seen with patients with indeterminate results, and all controlled viral replication spontaneously. The 25% of patients with an indeterminate result developed CMV disease. Viral relapse was associated with the failure to reconstitute CMV-specific CMI after the resolution of the first episode of CMV infection (P = .032)	QT-CMV can be a useful tool for identifying patients (i) at higher risk of developing infection after discontinuing antiviral prophylaxis, (ii) with late CMV infection who would benefit from appropriate antiviral interventions, and (iii) at higher risk of viral relapses. QT-CMV measurements taken within 1 mo post-transplantation are not revealing
Sood et al, 2018 [28]	Liver transplant (59)	QT-CMV was evaluated regularly until 6 mo post-transplant Only patients who had prior CMV exposure (pretransplant D+ or R+), 6-month QT-CMV data, and follow-up until 12 mo were considered	All 50 pts who had a reactive QT-CMV by month 6 (of them over 90% had a reactive result at 3 mo) remained CMV-free at 12 mo, while 3 (33.3%) of 9 patients with nonreactive QT-CMV developed late CMV infection (2/3 a CMV disease)	QT-CMV has an excellent negative predictive value for late CMV, suggesting patients who exhibit a robust ex vivo immune response at 6 mo can safely cease CMV monitoring Furthermore, >90% already express viral-specific immunity as early as 3 mo Antiviral prophylaxis could be discontinued early in these patients

(Continues)

TABLE 2 (Continued)

Author, year (reference)	Type of transplant population (no. of patients)	Design of study	Results	Authors' comment
Deborska-Materkowska et al, 2018 [29]	Kidney transplant (86)	This prospective study evaluated whether a specific viral T-cell response by QT-CMV allows for the better identification of recipients who are at high risk of CMV infection after prophylaxis withdrawal	QT-CMV assay yielded reactive results in 51 of 67 CMV-seropositive patients (76%) compared with 7 of 19 patients (37%) CMV-seronegative (P = .001). In the CMV-seropositive patients, infection occurred in seven of 16 recipients (44%) who were QT-CMV nonreactive and 8 of 51 recipients (16%) who were QF-CMV reactive. In the CMV-seronegative group, infection evolved in five of 12 recipients (42%) who were QF-CMV nonreactive and one of 7 recipients (14%) who were QF-CMV reactive. The multivariate analysis revealed that the nonreactive QT-CMV assay was an independent risk factor for postprophylaxis CMV infection	In kidney transplant recipients who received post-transplantation prophylaxis, negative QT-CMV results better defined the risk of CMV infection than initial CMV IgG status after prophylaxis withdrawal
Páez-Vega et al, 2018 [30]	SOT (overall 104; kidney, 51; and liver, 53)	This prospective study evaluates whether CMV-seropositive transplant patients with pretransplant-positive QT-CMV can spontaneously clear the CMV viral load without requiring treatment	The incidence of CMV replication and disease was 45.2% (47/104) and 6.7% (7/104), respectively. Of the total patients, 77.9% (81/104) did not require antiviral treatment, either because they did not have CMV replication (n = 57) or because they had asymptomatic CMV replication that could be spontaneously cleared (n = 24). Both situations were related to positive QT-CMV. However, 22.1% of the patients (23/104) received antiviral treatment, although only 7 of them did so because they had symptomatic CMV replication. These patients developed symptoms in spite of having pretransplant-positive QT-CMV	Around 80% of CMV-seropositive patients with pretransplant, positive QT-CMV did not require antiviral treatment. Nevertheless, other strategies such as performing an additional QT-CMV response determination at post-transplant time might provide more reliable information regarding the patients who will be able to spontaneously clear the viremia
Thompson et al, 2018 [31]	SOT (overall 49; kidney, 24; cardiac, 12; lung, 10; and liver, 3)	QT-CMV assay was performed in Western Australian SOT recipients to determine the relationship between CMV-specific immunity, DNAemia, and disease following cessation of antiviral prophylaxis	Asymptomatic CMV DNAemia was detected in 61% of patients but only two patients ultimately developed CMV disease, both of whom had negative QT-CMV responses. 94% of patients who had spontaneous resolution or stability of asymptomatic CMV viremia without any antiviral treatment had positive QT-CMV responses. Patients with nonreactive QT-CMV responses had earlier onset and higher level CMV DNAemia compared to those with positive QT-CMV responses	QT-CMV assay may help to decision making for the management of asymptomatic viremia while reducing costs and side effects of antiviral treatment in SOT recipients
Westal et al, 2019 [32]	Lung transplant (118)	Patients at risk of CMV infection were randomized 1:2 to either 5 mo or variable length valganciclovir prophylaxis (5-11 mo post-LTx), as determined by the QT-CMV assay. Patients with a negative QT-CMV assay (< 0.2 IU/mL) received prolonged valganciclovir prophylaxis	The incidence of CMV infection within 18 mo of lung transplant was significantly reduced in the QT-CMV directed arm (37% vs 58%, P = .03). Of the 80/118 patients who ceased antiviral prophylaxis at 5 mo, the incidence of DNAemia (> 600 copies/mL) within the blood was significantly reduced in patients with a positive QT-CMV assay compared with those without protective immunity (13% vs 67%, P = .0003), as was the incidence of severe DNAemia (> 10 000 copies/mL) (3% vs 50%, P < .001)	Cytomegalovirus immune monitoring allows an individualized approach to CMV prophylaxis and reduces late CMV infection within the lung allograft

Abbreviations: Allo-HSCT, allogeneic hematopoietic stem cell transplant; CMI, cell-mediated immunity; CMV ELISpot, CMV-specific enzyme-linked immunosorbent spot assay; D−, donor with negative CMV serology; D+, donor with positive CMV serology; QT-CMV, Quantiferon-CMV assay; R−, recipient with negative CMV serology; R+, recipient with positive CMV serology; ROC curve, receiver operating characteristic curve.

plasma, red blood cells), given the potential for passive transfer of antibody, and a pretransfusion sample should be tested when possible.[15] In the cases of suspected passive antibody acquisition, CMI assays may be useful in establishing true immunologic status.[16] This can be considered a feasible practice in recipients and in live donors, while in deceased donors indeterminate results may occur.[17]

In the majority of SOT patients, IGRAs can be performed at any time before and not earlier than 30 days after the transplant. In SOT experiences, IGRAs were performed before transplant, after transplant before CMV infection, or after CMV infection (Table 2).[18-32] Positive IGRAs, both before and after SOT, were variably predictive of a lower risk of CMV infection/disease, longer CMV-free period, spontaneous viral clearance, lower rate of CMV infection recurrence, and lower level of CMV DNAemia. CMI response is predictive of a very low risk of CMV infection and disease; therefore, it may be considered a safe suspension criterion of CMV monitoring and prophylaxis. A negative test before transplantation may predict CMV infection risk in the post-transplant period. Overall, these experiences seem to suggest the use of immune monitoring in combination with viral load monitoring to improve assessment of the individual's ability to control CMV.

Recommendations

- In both SOT donor and recipient, anti-CMV IgG should be evaluated before transplant (A II). Serology should be repeated at the time of transplantation when the donor or recipient is seronegative during the pretransplant evaluation (BIII). If equivocal serologic assay results are obtained in the donor or in the recipient, the transplant should be considered at high CMV risk of post-transplantation management decisions (BIII).
- Pretransplant evaluation of recipient CMV-specific CMI by a IGRA is recommended just before transplant when a living donor is utilized, or at the time of transplant indication when a deceased donor is planned (BII). Subsequently, IGRAs can be performed starting at least 30 days after transplant (BII). The frequency of the post-transplant CMI determination has not yet been defined.
- In patients with a persistent CMV-specific T-cell response, antiviral prophylaxis could be avoided or discontinued and viral monitoring interrupted (BII). If a CMV DNAemia is documented, waiting for a spontaneous viral clearance without treatment or using a shorter viral treatment may be the strategies of choice (BII). Conversely, an intensive viral monitoring and an aggressive prophylaxis or therapy are indicated if a poor CMV-specific T-cell response is documented (BII).

3.2 | What is the appropriate antiviral prophylaxis strategy?

3.2.1 | Allo-HSCT recipients

A systematic meta-analysis of the benefit of CMV prophylaxis in allo-HSCT has been published in 2009.[33] When prophylaxis was given during the pre-engraftment phase, CMV disease rates were significantly lower, but there was no significant impact in the overall mortality. In trials in which a post-engraftment prophylaxis was given, CMV disease rates and overall mortality rates were significantly lower. Adverse effects were more frequent with prophylaxis, mainly represented by neutropenia caused by ganciclovir.

After this meta-analysis, a number of controlled trials tested the efficacy of CMV prophylaxis in allo-HSCT with new antivirals (maribavir, brincidofovir, letermovir, valganciclovir) compared to old antivirals (acyclovir, valacyclovir) or placebo (Table 3).[34-39] Letermovir showed the best relative efficacy for CMV infection and the best option in terms of safety.[38,39] Overall, the antiviral prophylaxis did not significantly influence the risk of death although the use of letermovir was associated with a trend toward improved survival.

Recommendations

- Antiviral prophylaxis is recommended in all allo-HSCT recipients (AI) starting from the day of transplantation until day 100 after transplant or longer in case of prolonged immunosuppression (BII).
- In CMV R-neg, high-dose acyclovir or valacyclovir is recommended for the whole period of prophylaxis (AII).
- In CMV R-pos, letermovir should be adopted as best prevention approach starting early after transplant during the engraftment period and until day 100 from transplant (AI). In patients with persistent CMV infection risk after day 100, prophylaxis should be continued with high-dose acyclovir or valacyclovir (currently the use of letermovir prophylaxis is not allowed after day 100).

3.2.2 | SOT recipients

The efficacy of antiviral prophylaxis in SOT has been analyzed in a meta-analysis published in 2013.[40] Prophylaxis with acyclovir, ganciclovir, or valacyclovir compared with placebo/no treatment variably reduced the risk of CMV disease, CMV infection, and all-cause mortality, without reducing the risk of acute rejection or graft loss. The relative effect of acyclovir, ganciclovir, and valacyclovir on CMV disease and mortality was comparable among heart, kidney, and liver transplants in both CMV-positive and CMV-negative recipients of CMV-positive organs. The effect on CMV disease, all-cause mortality, and other outcomes was similar for valganciclovir and ganciclovir prophylaxis, while ganciclovir showed advantages compared with acyclovir in preventing CMV disease. No difference was demonstrated between ganciclovir and valganciclovir or between valacyclovir and ganciclovir/valganciclovir.

Prophylaxis and preemptive protocols after renal transplantation were systematically compared.[41,42] Prophylaxis was significantly more effective than preemptive therapy in reducing the episodes and the recurrence rates of CMV infection, but higher incidence of

TABLE 3 Results of controlled studies on antiviral prophylaxis in allo-HSCT recipients published in the last 10 years

Antiviral drug (Author, year of publication) [n. reference]	Type of study	Main results
Allogeneic HSCT		
Maribavir (Marty et al, 2011) [34]	Placebo-controlled, randomized, double-blind, multicenter phase 3 study	Maribavir prophylaxis did not prevent CMV disease when started after engraftment when compared with placebo. During the 100 d following transplantation, CMV infection rates as measured by pp65 antigenemia were lower in the maribavir group (26.4%) than in the placebo group (34.8%), but not when measured by plasma CMV DNA polymerase chain reaction (PCR) (27.8% vs 30.4%), nor by initiation of treatment against CMV (30.6% vs 37.4%). Maribavir was largely well-tolerated, and there was no difference in the proportion of patients with adverse events leading to study drug discontinuation and serious adverse events compared with placebo Among the possible reasons of maribavir prophylaxis failure inadequate dose of maribavir, exclusion of high-risk patients from the trials, low CMV disease rates in the control group, and too much sensitivity of the PCR CMV assay have been considered
Brincidofovir (Marty et al, 2013) [35]	Patients were assigned in a 3:1 ratio to five sequential study cohorts according to a dose-escalating, double-blind design. Phase 2 study	Oral formulation of brincidofovir failed to prevent clinically significant CMV infection. However, the incidence of CMV events was significantly lower among patients who received brincidofovir at a dose of 100 mg twice weekly than among patients who received placebo (10% vs 37%). Diarrhea was a major adverse event in patients receiving brincidofovir and was significantly higher at doses of 200 mg weekly or higher
Brincidofovir (Marty et al, 2018) [36]	Randomized, double-blind, placebo-controlled phase 3 Trial	452 adult CMV-seropositive HSCT recipients received oral brincidofovir or placebo until week 14 post-HSCT. Serious adverse events were more frequent among brincidofovir recipients (57.1% vs 37.6%), driven by acute graft-vs-host disease (32.3% vs 6.0%) and diarrhea (6.9% vs 2.7%). Week 24 all-cause mortality was 15.5% among brincidofovir recipients and 10.1% among placebo recipients
Valganciclovir (Boeckh et al, 2015) [37]	Randomized, double-blind trial, multicenter phase 3 trial	184 HCT recipients at high risk of late CMV disease received 6 mo of oral valganciclovir or placebo valganciclovir prophylaxis was not superior in reducing the composite end point of CMV disease, invasive bacterial or fungal disease, or death when compared with PCR-guided preemptive therapy
Letermovir (Chemaly et al, 2014) [38]	Placebo-controlled, randomized, double-blind, sequential cohorts, multicenter phase 2 study	131 HSCT patients received oral letermovir (at a dose of 60, 120, or 240 mg per day, or matching placebo) for 12 wk after engraftment. The incidence of prophylaxis failure with letermovir, as compared with placebo, was 48% vs 64% at a daily letermovir dose of 60 mg, 32% at a dose of 120 mg, and 29% at a dose of 240 mg. The safety profile of letermovir was similar to placebo, with no indication of hematologic toxicity or nephrotoxicity
Letermovir (Marty et al, 2017) [39]	Placebo-controlled, randomized, double-blind, multicenter phase 3 study	Among 495 patients with undetectable CMV DNA at randomization, fewer patients in the letermovir group than in the placebo group had clinically significant CMV infection or were imputed as having a primary end point event by week 24 after transplantation (37.5% vs 60.6%). The letermovir effect in the prevention of clinically significant CMV infection was observed both in patients at high risk and in patients at low risk of CMV disease. The frequency and severity of adverse events were similar in the two groups. All-cause mortality in letermovir and placebo groups was 10.2% and 15.9% ($P = .03$) at 24 wk from transplantation, respectively, and 20.9% and 25.5% ($P = .12$) at week 48 after transplantation, respectively. The lower mortality among letermovir recipients than among placebo recipients was more pronounced among high-risk patients than among low-risk patients

late-onset CMV infection and neutropenia was observed with prophylaxis. Both approaches were comparable in reducing the risk of CMV disease, while no significant differences were observed in the risks of mortality, acute rejection, graft loss, neutropenia, or other infections. These results were confirmed in a recent randomized clinical trial where renal transplant recipients receiving prophylaxis experienced less CMV infections (11.5% vs 39.7%) and diseases (4.7% vs 15.9%) compared with those who received a preemptive approach.[43]

A systematic review in liver transplant recipients showed that, irrespective of donor/recipient CMV serostatus, CMV disease, acute cellular rejection, and mortality were similar with prophylaxis and preemptive strategies, but graft loss was significantly lower in the prophylaxis group.[44] In view of the higher rates of CMV disease in liver transplant recipients who received prophylaxis with valganciclovir compared to oral ganciclovir, the US FDA did not approve valganciclovir for CMV prophylaxis in liver transplant recipients.

When used for prophylaxis, the usual dose of valganciclovir is 900 mg daily; however, a systematic review on low-dose (450 mg/day) prophylaxis schedules in renal transplant recipients showed comparable efficacy and safety profiles.[45]

In light of the observation of late-onset CMV disease, longer periods of CMV prophylaxis have been suggested. In a study of kidney transplant,[46] 200 days of antiviral prophylaxis was associated with lower incidence of CMV disease compared with 100 days of prophylaxis.

Recommendations

- In SOT, there is no clear evidence of benefit from universal CMV prophylaxis with antivirals (CI). Antiviral prophylaxis is justified in high-risk patients, that is, in R-neg receiving transplant from a D-pos, in patients undergoing antirejection treatment, or in R-pos in which CMV monitoring for a preemptive strategy is not feasible (BII). In these patients, valganciclovir 450-900 g/day or intravenous ganciclovir (5 g/kg/day), adjusted according to the renal function, is recommended (BI).
- Prophylaxis should be started within 10 days post-transplant and continued until 3-6 months post-transplant (BII).

3.3 | How should a preemptive strategy be implemented?

The studies which compared the efficacy and safety of different molecules given as preemptive therapy in allo-HSCT and SOT populations did not demonstrate significant efficacy differences (Table 4).[47-50] Neutropenia was more frequent with ganciclovir and valganciclovir.

The mainstay of preemptive therapy is monitoring of CMV DNAemia by real-time PCR assays of the at-risk patients and the initiation of antiviral treatment when a viral load threshold is reached, so that the infection does not progress to CMV disease.[1] CMV DNA may be extracted and quantified from either plasma or whole blood. While a correlation between CMV DNA levels in the two biologic matrices has been demonstrated, plasma DNAemia is about 1 $\log_{10}$ lower than whole blood DNAemia. In addition, a recent retrospective, multicenter study in allo-HSCT recipients reported different CMV DNA kinetics in whole blood vs plasma, and a prolonged persistence of CMV DNA following ganciclovir treatment was observed in plasma.[51] The same data have been observed in a kidney transplant population (unpublished data). Therefore, DNAemia monitoring using plasma may expose patients to unnecessary prolonged period of antiviral therapy with a possible increase in toxicity.

Since 2010, when the World Health Organization (WHO) International Reference Standard for CMV DNA quantification became available, laboratory-specific quantitative assay systems can be calibrated and the DNAemia results reported as IU/mL.[52]

Consensus viral load thresholds to initiate preemptive therapy is a debated issue for both allo-HSCT and SOT not only due to the highly variable infectious risk of the different types of transplant and the different perception of risk by the transplantologists, but also due to the widespread use of different laboratory developed assays and paucity of assays calibrated to the WHO International Standard. Therefore, individual centers are forced to define their own criteria for the definition of appropriate thresholds in their patient

TABLE 4 Results of controlled studies on anti-CMV preemptive therapy in allo-HSCT and SOT recipients published in the last 10 years

Antiviral drug (Author, year of publication) [n. reference]	Type of study and type of transplant	Main results
Valganciclovir vs ganciclovir (Chawla et al, 2012) [47]	Pilot prospective randomized clinical trial. Allo-HSCT	37 enrolled patients. Oral valganciclovir was not inferior in efficacy to intravenous ganciclovir as preemptive therapy, with rates of viral clearance at 28 d of 89.5% and 83%, respectively. Toxicities were similar between the two arms. No patients developed CMV disease
Valganciclovir vs ganciclovir or foscavir (Ruiz-Camps et al, 2011) [48]	2-year prospective, comparative cohort study. Allo-HSCT	237 episodes of preemptive therapy for active CMV infection were collected in 166 allo-HSCT recipients. No statistically significant differences were found when valganciclovir was compared with ganciclovir or foscarnet
Maribavir vs valganciclovir (Maertens et al, 2016) [49]	Randomized phase II study. Allo-HSCT and SOT	119 and 40 patients received maribavir and valganciclovir, respectively, with similar efficacy of the two treatments at clearing CMV viremia. Gastrointestinal adverse events occurred more frequently with maribavir and neutropenia was more frequent with valganciclovir
Maribavir (Papanicolaou et al, 2018) [50]	Randomized, dose-ranging, double-blind, phase 2 study. Refractory or resistant CMV infections in allo-HSCT or SOT	Twice-daily dose-blinded maribavir 400, 800, or 1200 mg for up to 24 wk. Overall, 80/120 (67%) patients achieved undetectable CMV DNA within 6 wk of treatment, with no dose-related difference in response. Out of 25 patients in which CMV infection recurred on-treatment in 13 viral mutations conferring maribavir resistance were documented. Maribavir was discontinued due to adverse events in 41/120 (34%) patients, and 17/41(41%) discontinued due to CMV infections. Dysgeusia was the most common adverse event and occurred in 65% of patients but led to maribavir discontinuation in only 1 patient

populations and the comparison between different strategies is difficult. Collaborative studies to determine consensus threshold in IU/mL are needed.

The use of viral load kinetics (ie, doubling time) based on a tailored frequency of DNAemia testing proved to impact the effectiveness of an antiviral preemptive strategy in high-risk groups. Viral load kinetic may be a better indicator to start treatment than any absolute viral load value. It should be also considered that the variability of sensitive molecular tests is high particularly for low CMV DNAemia loads (<1000 IU/mL), and changes should be greater than 3-fold (0.5 log10 IU/mL) in order to demonstrate significant variation in viral replication.[53]

The different mechanism of action of the antiviral drugs should be considered in the interpretation of the virological results. Acyclovir, valacyclovir, ganciclovir, valganciclovir, and foscarnet inhibit replication of CMV DNA by interfering with the function of CMV DNA polymerase, and conversely, letermovir inhibits terminase complex subunit pUL56 at a stage of maturation and packaging of viral particles distal to viral DNA synthesis.[54] Consequently, free CMV DNA fragments may remain detectable early on in the blood and breakthrough CMV DNAemia might be of difficult interpretation in patients receiving treatment with letermovir.

Recommendations

Allo-HSCT and SOT recipients

- A preemptive approach with an appropriate monitoring of CMV DNAemia is recommended in both allo-HSCT and SOT, regardless of the use of antiviral prophylaxis (AII). The PCR assay results should be preferably reported as International DNA Units (IU) instead of DNA copies.
- Since CMV DNAemia significantly differs in plasma and in whole blood, the same specimen should be used for a sequential reliable monitoring (AII).
- Whole blood DNAemia should be preferred for guiding preemptive treatment because plasma DNAemia might persist despite an adequate viral control, inducing an inappropriate antiviral treatment extension (BII).

Allo-HSCT recipients

- In standard risk allo-HSCT (ie, patients with negative CMV DNAemia and not receiving immunosuppressive therapy for GVHD), DNAemia should be determined at least once a week in the first trimester post-transplant, once every other week in the second trimester, and once every month until GVHD prophylaxis withdrawal (BII). In high-risk allo-HSCT (ie, patients with CMV DNAemia positivity or receiving immunosuppressive therapy for any cause), intensification of the monitoring schedule (twice a week) should be applied along the whole high-risk period (BII).
- Preemptive treatment (ganciclovir or valganciclovir with foscarnet as second line) should be initiated in case of any whole blood CMV DNA > 10 000 copies/mL or plasma CMV DNA > 1000 copies/mL (BIII).
- A lower cutoff may be considered in allo-HSCT patients with the conditions of high risk of viral disease, that is, early infection (within the first 30 days after transplant), cord blood transplant, active anti-GVHD treatment after a transplant from haploidentical or mismatched unrelated donor, and seropositive recipients with seronegative donor (BIII). At the threshold attainment, a further early monitoring (within a couple of days) of DNAemia is suggested as a useful help for the initiation of treatment (BIII). At least a 3-fold increase in DNAemia should be considered significant.
- Preemptive therapy should be discontinued in conjunction with the CMV DNAemia clearance in two consecutive tests at an interval of at least 3-4 days (BII).
- "Maintenance treatment" with reduced doses should be discouraged due to the higher risk of selection of drug-resistant mutants (BIII).

SOT recipients

- In standard risk SOT recipients (ie, patients with negative CMV DNAemia and not receiving antirejection treatment), DNAemia should be determined at least once a week in the first trimester post-transplant, once every other week in the second trimester, and once every month up to 1 year in the absence of clinical indications (BII). In high-risk SOT recipients (ie, with primary infection, during antirejection treatment, or in the presence of additional infection risk factors, such as T-cell depletion), intensification of the monitoring schedule (twice a week) should be applied (BII).
- Preemptive treatment (ganciclovir or valganciclovir with foscarnet as second line) should be initiated in case of any whole blood CMV DNA > 100 000 copies/mL or plasma CMV DNA > 10 000 copies/mL (BIII).
- In D-pos/R-neg, SOT intensification of the monitoring schedule (twice a week) should be applied (BII) to avoid delays in starting antiviral treatment (BIII). In case of any positive DNAemia in SOT patients undergoing antirejection treatment, antiviral treatment should be administered until DNA assay becomes negative (BIII).

3.4 | Is intravenous Immunoglobulin useful in prophylaxis of CMV infection and disease?

A systematic review of clinical trials did not provide evidence that polyclonal intravenous immunoglobulins (IVIG) or CMV-specific IVIG are useful alone or in combination with antiviral agents in primary prophylaxis of CMV infection in allo-HSCT.[55]

According to a systematic review, the use of IVIG compared with placebo/no treatment in SOT was not associated with a significant difference in the risk of CMV disease, CMV infection, or all-cause mortality while a significant reduction in the risk of death from CMV disease was observed.[56]

After the publication of these reviews, no relevant data have been published on the use of IVIG in transplant populations.

Recommendations

- There are limited data to support the use of IVIG or CMV-specific IVIG for prophylaxis both in allo-HSCT and in SOT (CII)

3.5 | Prophylaxis and treatment with adoptive immunotherapy

Adoptive transfer of ex vivo generated CMV-specific T lymphocytes (CMV-CTL) has the potential to restore immunity, prevent CMV, and circumvent the need for pharmacologic therapies.[1] The main results of trials of CMV-CTL therapy for CMV infection in allo-HSCT recipients published in the last 5 years are described in Table 5.[57-60] Overall, these studies showed that CMV-CTL therapy was safe, not associated with an increase in GVHD and associated with a reduction in the viral burden. Post-infusion in vivo expansion of CMV-CTLs was obtained in most of the patients. The process of generating effector cells for each patient can take several weeks; therefore, there is increasing interest in using HLA-matched third-party banked T cells. This method could also allow generation of cells active against multiple viruses including CMV, Epstein-Barr virus, and adenovirus.[61-63] However, the use of third-party T cells is still experimental and further safety and efficacy data are needed.

Few anecdotal case reports demonstrating the clinical use of CMV-specific T cells for resistant/refractory CMV infection in SOT recipients have been reported.[64-67] While donor-derived material is used for the adoptive CTL therapy in allo-HSCT, in the context of SOT recipients autologous immune cells may be used to generate an effective T-cell therapy. In a prospective study, 13 SOT recipients with recurrent or ganciclovir-resistant CMV infection received in vitro expanded autologous CMV-CTLs and 11 (84%) of them experienced an overall clinical improvement, including resolution or reduction in CMV DNAemia and end-organ disease and/or the cessation or reduced use of antiviral therapy.[68]

Recommendations

- Currently, infusion of adoptive CMV-CTL cannot be considered a standard practice in allo-HSCT However, CMV-CTL therapy might be suggested in the following high-risk allo-HSCT populations: recipients of HLA-haploidentical grafts when the prevention of GVHD is based on the ex vivo T depletion of the grafts by a positive immunoselection of the CD34+ cells and in the event of the addition of serotherapy over the conditioning

TABLE 5 Results of phase I-II trials of adoptive cellular therapy for CMV infection in allo-HSCT published in the last 5 years

Author, year of publication [reference]	Main results
Koehne et al, 2015 [57]	17 allo-HSCT recipients with CMV viremia or clinical infection persisting despite prolonged treatment with antiviral drugs received allogeneic T cells sensitized in vitro against a pool of pentadecapeptides spanning the sequence of CMVpp65. T-cell infusions were well-tolerated without toxicity or GVHD. Of 17 patients treated with transplant donor (n = 16) or third-party (n = 1) CMV-CTLs, 15 cleared viremia, including 3 of 5 with overt disease. In responding patients, the CMV-CTLs infused consistently proliferated and could be detected for period of 120 d to up to 2 y after infusion
Pei et al, 2017 [58]	CMV clearance within 4 wk CMV-CTL transfer without recurrence was evaluated in 32 patients with refractory CMV infection who received adoptive CMV-CTL infusion following haploidentical HSCT. The phenotypical and functional characteristics of CMV-specific CTL were analyzed before and after cellular therapy, and these characteristics were compared with those of other 32 patients with nonrefractory CMV infection after haploidentical HSCT. Compared to nonrefractory CMV-infected patients, CMV-specific CD8+ CTL in refractory CMV-infected patients exhibited a reduced capacity to produce the cytokines IL-2 and TNF-α. In the refractory cohort, 27 of the 32 treated patients exhibited CMV clearance within 4 wk after adoptive CTL transfer without recurrence. Cellular therapy was followed by in vivo expansion and improvement in the cytokine production and proliferation ability of the CMV-specific T cells. Neither the quantity nor the function of CMV-specific CTL was restored in the remaining 5 patients who showed CMV recurrence 4 wk after adoptive T-cell transfer
Withers et al, 2017 [59]	A prospective study of 28 allo-HSCT patients with persistent or recurrent CMV after standard therapy. Patients were treated with infusions of partially HLA-matched, third-party, ex vivo expanded CMV-CTLs (total = 50 infusions) at a median of 75 d post-HSCT. At 12 mo, the cumulative incidence of overall response was 93%. CMV-specific T-cell immunity rose significantly and coincided with a rise in CD8+ terminal effector cells
Neuenhahn et al, 2017 [60]	Allo-HSCT patients with drug-refractory CMV infection and lacking virus-specific T cells were treated with a single dose of ex vivo major histocompatibility complex-Streptamer-isolated CMV epitope-specific donor T cells. Forty-four allo-HSCT patients receiving a T-cell-replete (D+ repl; n = 28) or T-cell-depleted (D+ depl; n = 16) graft from a CMV-seropositive donor were screened for CMV-specific T-cell immunity. Eight D+ depl recipients received adoptive T-cell therapy from their stem cell donor. Complete and partial virological response rates were 62.5% and 25%, respectively. Owing to longsome third-party donor identification, only 8 of the 57 CMV patients transplanted from CMV-seronegative donors received CMV-CTLs from partially HLA-matched third-party donors

Abbreviations: CMV-CTL, CMV-specific cytotoxic T lymphocytes; HLA, human leukocyte antigen.

regimen with either ATG or alemtuzumab; recipients of unrelated cord blood transplant; and patients under intensive and prolonged immunosuppressive treatment because of either acute or chronic GVHD (BII).
- The use of CMV-CTL therapy is still to be considered experimental in SOT; therefore, no recommendation can be given.

4 | CONCLUSIONS

In this report, an EP judged whether the body of evidence was sufficient to provide recommendations regarding pretransplant risk definition, and post-transplant virological and immunological monitoring, prophylaxis, and therapy of CMV infection in allo-HSCT and SOT recipients. The lack of randomized clinical trials to assess some diagnostic procedures and antiviral intervention represents uncertainty in the optimization of virological management, thus forcing the panel to use the methods of consensus for shaping some recommendations. Indeed, the multidisciplinary format represented a unique and valuable feature of this consensus project.

CONFLICT OF INTEREST

C. Girmenia has received honoraria from Gilead Sciences, Astellas Pharma, Basilea, MSD, Pfizer Pharmaceuticals, and Celgene. T. Lazzarotto has received honoraria from MSD. F. Bonifazi has received honoraria from MSD, Neovii, Jazz, Pfizer, Novartis, Jansen, Dompe, and Incyte. F. Patriarca has received honoraria from Janssen, Celgene, MSD, Italy; and travel, accommodations, and expenses from Celgene, Jazz, and Med. G. Irrera, F. Citterio, and E. Gringeri declared no conflict of interest. F. Ciceri has received honoraria from MolMed, MSD, Jazz, and Biotest. F. Aversa has received honoraria from Gilead Sciences, Pfizer, Astellas, Roche, Novartis, Basilea, and MSD. U. Cillo has received honoraria from Novartis and Sanofi; and travel, accommodations, and expenses from J&J and Pfizer. E. Cozzi has received honoraria from Astellas, Novartis, and Biotest. F. Baldanti has received honoraria from MSD, Biotest, Shire, and Humabs. P. Clerici and R. Cavallo have received honoraria from MSD. G. Barosi has received honoraria from MSD and Novartis. P. Grossi has received honoraria from MSD, Biotest, Paratek, Angelini, Gilead Sciences, Becton Dickinson, Pfizer, Shire, and Nordic Pharma.

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