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Prophylaxis vs preemptive therapy in prevention of CMV infection: new insight on prophylactic strategy after allogeneic hematopoietic cell transplantation

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Abstract

Cytomegalovirus (CMV), the beta-human herpesvirus type 5 (HHV-5), is a major cause of morbidity in immunocompromised hosts, especially recipients of allogeneic hematopoietic cell transplantation (HCT) or solid organ transplantation. The standard-of-care approach to CMV prevention based on CMV surveillance-guided preemptive therapy is being challenged by the recent approval of letermovir (LMV) for primary prophylaxis. Real-word clinical data show dramatic improvement in the reduction of risk of CMV infection and any CMV viremia in all studies performed so far. LMV is the drug that is breaking the paradigm of preemptive therapy with shift to prophylaxis. A summary of reported data presented in 2019 annual meetings of American Society of Transplantation and Cellular Therapy (ASTCT), European Society for Blood and Marrow Transplantation (EBMT) and American Society of Hematology (ASH), as well as already published results, is presented in this review. A total number of 401 adult high-risk patients on primary prophylaxis after HCT were reported in 11 studies up to January 1, 2020. It was shown that fewer patients in the LMV arms had any CMV reactivation or need for CMV treatment compared with the any other prophylactic or preemptive approaches. In conclusion, LMV is much highly effective than CMV-guided preemptive therapy in preventing CMV infection and CMV disease. The use of LMV in prophylaxis results in an improvement in overall survival during the first 24 and 48 weeks. LMV has a favorable safety profile, as it does not cause myelotoxicity. Current guidelines of European Conference on Infections in Leukemia (ECIL7) recommend LMV for the use in prophylaxis of CMV infection in patients after allogeneic hematopoietic cell transplant.

Keywords:
cytomegalovirus, letermovir, prophylaxis, preemptive therapy, transplantation

Introduction

Cytomegalovirus (CMV), the beta-human herpesvirus type 5 (HHV-5), is a major cause of morbidity in immunocompromised hosts, especially recipients of allogeneic hematopoietic cell transplantation (HCT) or solid organ transplantation (SOT). On the other hand, primary infection with CMV in healthy individuals is usually asymptomatic, or it manifests as a self-limited febrile illness, such as mononucleosis-like syndrome.

Primary CMV infection or reactivation during immune suppression is associated with increased morbidity and mortality. CMV infection is a serious condition for immune system. It can adversely affect transplant outcomes directly or indirectly. Direct increased organ toxicity is the effect of the infection itself, while indirect toxicity is caused by associated side effects of antiviral therapy. This leads to a higher risk of bacterial and fungal infections. The most frequent clinical manifestations of CMV infection and disease in immunosuppressed patients are pneumonia, enteritis, bone marrow suppression, hepatitis, and retinitis [1]. It has been proven that CMV seropositive status, CMV infection, and CMV disease decrease survival after HCT [2, 3, 4].

As it is of utmost importance to prevent CMV infection and CMV disease, this paper was aimed to present and compare the strategies of prophylaxis and preemptive treatment against CMV after allo-HCT, with focus on (analysis of) current evidence-based possibilities of prevention of CMV infection reported in 2019. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by the author.

Definitions

Recently, updated definitions on CMV infection, CMV resistant infection, CMV disease, and CMV-resistant disease were published [1, 5, 6, 7]. Briefly:

- CMV infection is defined as virus isolation or detection of viral proteins (antigens) or nucleic acid in any body fluid or tissue specimen.
- CMV replication indicates evidence of viral multiplication and is sometimes used instead of CMV infection.
- Primary CMV infection is defined as the first detection of CMV infection in an individual who has no evidence of CMV exposure.
- Recurrent CMV infection is defined as new CMV infection in a patient with previous evidence of CMV infection who has not had virus detected for an interval of at least 4 weeks during active surveillance. Recurrent infection may result from reactivation of latent virus (endogenous) or reinfection (exogenous).
- CMV reinfection is defined as detection of a CMV strain that is distinct from the strain that caused the initial infection.

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- CMV reactivation is likely if the two viral strains (prior and current strain) are found to be indistinguishable either by sequencing specific regions of the viral genome or by using various molecular techniques that examine genes known to be polymorphic.
- Symptomatic CMV infection is diagnosed in patients developing symptoms (fever with or without bone marrow suppression) and who have CMV virions, antigens, or nucleic acid detectable but with no sign of CMV end-organ disease.
- CMV disease is diagnosed in patients with symptoms and/or signs from the affected organ together with the detection of CMV by a test with appropriate sensitivity and specificity from an organ in a biopsy or samples from other invasive procedures, with exception for CMV retinitis, for which typical findings by ophthalmologic examination are sufficient.
- Refractory CMV infection means CMV viremia that increases (>1 $\log_{10}$ increase in CMV DNA levels) after at least 2 weeks of appropriately dosed antiviral therapy.
- Probable refractory CMV infection means persistent viral load (CMV viral load at the same level or higher but <1 $\log_{10}$ increase in CMV DNA levels) after at least 2 weeks of appropriately dosed antiviral therapy.
- Refractory CMV end-organ disease involves worsening in signs and symptoms or progression into end-organ disease after at least 2 weeks of appropriately dosed antiviral therapy.
- Probable refractory CMV end-organ disease involves lack of improvement in signs and symptoms after at least 2 weeks of appropriately dosed antiviral drugs.
- Antiviral drug resistance involves viral genetic alteration that decreases susceptibility to one or more antiviral drugs.

Epidemiology of CMV infection and CMV disease after HCT

Detailed analysis of incidence of CMV recurrence in groups of immunocompromised patients showed that median rate of CMV infection (recurrence) was estimated to be 37% after allo-HCT and 12% after auto-HCT, 5% in non-transplant hematological malignancies, 14% in recipients of anti-CD52 therapy, 30% in SOT recipients, and 21% in primary immunodeficiencies. The highest risk of CMV infection and CMV disease after HCT was reported for CMV-seropositive recipients (R), regardless on donor (D) serostatus. The odds ratio for CMV infection was higher for CMV-serostatus R+ vs R- transplants (odds ratio [OR] = 8.0), CMV-serostatus D-/R+ vs D+/R+ transplants (OR = 1.2), unrelated/mismatched vs matched sibling donor transplants (OR = 1.6), and acute graft versus host disease (GVHD) vs others (OR = 3.2) [8]. Recent nationwide analysis in Poland showed the incidence of CMV infection of 28.9% in pediatric and 24.7% in adult allo-HCT recipients [9, 10, 11].

Strategies for managing CMV infection following HCT

Current universal (nonpharmacological) management strategies to prevent primary CMV infection in CMV-seronegative recipients of allo-HCT include donor selection, transfusion policy (i.e., tested safe blood products, including leukodepleted and filtered red cell and platelet concentrates), and non-specific hygiene preventive measures in hospital environment, including training for patients (e.g., to perform regular handwashing and to avoid sharing cups, glasses, and eating tools) (Tab. I).

Recommendations for pre-transplant setting are based on testing of all patients and donors for CMV IgG antibodies. The choice of a donor includes CMV-seronegative donor for a CMV-seronegative recipient and CMV-seropositive donor for a CMV-seropositive recipient (if possible) in the setting of myeloablative unrelated allo-HCT; however, there is no priority in the donor CMV serostatus for a CMV-seropositive recipient designed for non-T-cell-depleted haplo-HCT with post-transplant cyclophosphamide (PTCy) [6].

Current pharmacological management strategies to prevent CMV infection (primary or reactivation) or CMV disease in the recipient of allo-HCT include prophylaxis or preemptive therapy:

- Prophylaxis – it is a strategy where antiviral agents are given to a patient to prevent a primary, reactivated, or recurrent CMV infection.
- Preemptive therapy – it is a strategy where antiviral agents are given for an asymptomatic CMV infection detected by a specific screening assay [5, 6].

Antiviral anti-CMV prophylaxis

In order to prevent CMV disease, early CMV replication should be prevented. Retrospective analysis of seropositive patients monitored by qPCR has shown in multivariate analysis a significant effect of presence of any level of CMV viremia on all-cause mortality and non-relapse mortality both during early and late post-transplant period up to day +365, even despite the use of preemptive therapy [4]. The fact that CMV replication is associated with mortality is the principal reason to use prophylaxis against CMV infection after allo-HCT. Apart from adverse effects of CMV replication, another reason is that CMV seropositivity in the patient decreases survival [2, 3].

Prophylaxis of CMV infection was usually not being used so far in allo-HCT, because data from previous studies and strategy from many years have shown that:

- Aciclovir/valaciclovir are not effective enough.
- Ganciclovir and foscarnet are effective but toxic in HCT recipients.
- Valganciclovir is effective in SOT (but causes myelosuppression, thus is used significantly limited in HCT recipients).

Table I. Strategies for managing CMV infection following hematopoietic cell transplantation

Strategy	Management
Universal prophylaxis	To prevent CMV infection/reactivation
Risk-adapted prophylaxis	To prevent CMV infection/reactivation in high-risk subgroups
Preemptive therapy	Treatment of (a)symptomatic CMV infection detected by a screening assay to prevent CMV disease
Therapy	Treatment of end-organ CMV disease

- Drug resistance and intolerance remain as problems.
- Failure of Phase III studies for prophylaxis with maribavir (MBV) and brincidofovir (BCV).

Current European Conference on Infections in Leukemia (ECIL7) recommendations on CMV prophylaxis in allo-HCT are presented in table II. The main pitfall of prophylaxis strategy is unnecessary treatment of patients who will not develop CMV infection or disease (Tab. III). Because of toxicity and limited efficacy, there is no ideal agent available due to: myelosuppression (ganciclovir) and renal toxicity (foscarnet); more bacterial and fungal infection, and breakthrough infection. Additionally, no improvement for overall survival (OS) was shown so far, while delayed immune reconstitution, late CMV disease, and potential for development of resistance were observed with the use of available anti-CMV antivirals.

Preemptive therapy against CMV disease

Preemptive therapy is regarded as the standard strategy for CMV prevention after allo-HCT, and current guidelines recommend this approach [5, 6, 12, 13]. Using this strategy, patients are monitored weekly for CMV reactivation using CMV nucleic acid test (NAT) by PCR. Detection of asymptomatic CMV reactivation above a "viral load threshold" prompts the initiation of preemptive treatment to prevent progression to clinical disease.

Rationale for monitoring preemptive treatment is based on (A) availability of sensitive diagnostic test, recently WHO standardized [14]; (B) predictivity of a positive result for development of CMV disease, except for gastrointestinal infection and retinitis; (C) knowledge that early intervention can prevent disease [15]; and (D) availability of an effective (and relatively safe) antiviral drug.

Current ECIL7 first-line preemptive therapy recommendations for allo-HCT recipients include [6]:

- Either IV ganciclovir or foscarnet can be used for first-line preemptive therapy.
- Valganciclovir can be used in place of IV ganciclovir or foscarnet (except in patients with severe gastrointestinal GVHD).
- The combination of foscarnet+ganciclovir is not recommended.
- The choice of drug depends on time after HCT, risk of toxicity, and previous antiviral drug exposure.

The pitfall of preemptive therapy is that the strategy of viremia-guided preemptive therapy still allows for CMV reactivation. Although preemptive treatment of asymptomatic CMV reactivation is efficacious in reducing tissue-invasive CMV disease, emerging data suggest a negative long-term effect of CMV replication [4].

Anti-CMV antivirals

Currently available anti-CMV drugs include (val)ganciclovir, foscarnet, cidofovir, and acyclovir (plus valacyclovir and famciclovir). Three new antiviral agents have emerged in recent times, including letermovir (LMV), MBV, and BCV, enhancing ability to prevent and treat CMV. All these drugs were efficacious in prophylaxis in Phase II studies [17, 18, 19]; however, BCV [20] and MBV [21] failed in Phase II studies. While LMV is already licensed in the USA and Europe, the role of MBV and BCV is still investigational, although MBV was shown to be effective in preemptive treatment [22] and for refractory and resistant CMV infection [23].

LMV belongs to a new class of compounds. Chemically, it is 3,4-dihydro-quinazoline-4-yl-acetic acid derivative compound. It inhibits CMV through a novel mechanism involving the viral terminase

Table II. Current ECIL7 recommendations on CMV prophylaxis in allogeneic HCT

Drug	Grading	References	Comment
Letermovir	AI	Marty et al., N Engl J Med 2017	
Valaciclovir	BI	Ljungman et al., Blood 2002 Winston et al., Clin Infect Dis 2003	Association with preemptive strategy; causes severe myelo-suppression
Ganciclovir	CI	Winston et al., Ann Intern Med 1993 Goodrich et al., Ann Intern Med 1993	Causes myelosuppression
Aciclovir	CI	Prentice et al., Lancet 1994	Less efficient than valaciclovir
Foscarnet	DII	Ordemann et al., Ann Hematol 2000 Bregante et al., Bone Marrow Transplant 2000	

Grading: A – strongly recommended; B – generally recommended; C – optionally (weakly) recommended; D – not recommended; I – based on randomized trial; II - based on nonrandomized clinical studies.

Table III. CMV management strategies: advantages and disadvantages of prophylaxis and preemptive therapy

	Advantages	Disadvantages
Antiviral prophylaxis	Efficacious for CMV disease prevention Reduce early CMV reactivation Can prevent direct and indirect effects Viral load monitoring not required CMV disease may occur without detectable CMV DNAemia	High rate of myelo- and nephrotoxicity Risk of overtreatment Risk of delayed-onset "post-prophylaxis" CMV infection and disease Drug cost May delay CMV-specific immune reconstitution
Preemptive therapy	Efficacious for CMV disease prevention Reduce overall drug cost Reduce risk of drug toxicity (e.g., neutropenia) Targets patients at the highest risk May improve CMV-specific immune reconstitution	Does not prevent early CMV reactivation Logistical nature of CMV surveillance and clinical follow-up Potential to miss cases of CMV disease not preceded by DNAemia or antigenemia Relies on availability of CMV testing Concern for drug resistance

Modified from Razonable, COID 2018 [16].

complex and shows potent anti-CMV activity *in vitro* and *in vivo*, but not against other viruses. No cross-resistance with drugs currently used in the treatment of CMV was observed [24].

When administered orally, its bioavailability is 94% in healthy individuals. In allo-HCT recipients, it is only 35%; however it is increased to 85% in the presence of cyclosporine. It is excreted 93% as feces and 70% as unchanged drug. Owing to only a minimal renal excretion, there is no need for renal dose adjustments.

After successful Phase III study [25], its clinical use is licensed by US Food and Drug Administration (FDA) (11 August 2017) followed by European Medicines Agency (EMA) (10 November 2017) for clinical use for antiviral prophylaxis to prevent CMV in at-risk CMV-seropositive allo-HCT recipients. Prior to starting prophylaxis, a negative viral load should be documented. During LMV prophylaxis, CMV PCR surveillance is necessary to monitor breakthrough CMV infection. The recommended dose of LMV is 480 mg once daily or 240 mg once daily in the presence of cyclosporine for prophylaxis. This is because cyclosporine increases LMV levels. Another potential important interaction is reduction of voriconazole levels by LMV.

Current considerations for use include necessity to document a negative viral load prior to starting prophylaxis. CMV PCR surveillance should be performed to monitor breakthrough CMV infection during LMV prophylaxis. Additionally, potential interactions (cyclosporine increases LMV levels, LMV reduces voriconazole levels, and others) should be checked.

LMV is approved by FDA and EMA as antiviral prophylaxis for the prevention of CMV in allogeneic HCT recipients, while it is not approved for preemptive treatment of asymptomatic CMV infection and treatment of CMV disease, including those due to GCV-resistant virus, and secondary CMV prophylaxis, and in children.

Real-world experience with LMV in primary prophylaxis of CMV after HCT in adult patients

In order to analyze real-world evidence of LMV use for CMV prophylaxis in clinical practice, review of data reported in studies on primary prophylaxis with LMV in adults, presented on major hematology/HCT (American Society of Transplantation and Cellular Therapy (ASTCT/TCT); European Society of Blood and Marrow Transplantation (EBMT); and American Society of Hematology (ASH)) annual meetings in 2019, supplemented with two papers published in 2019, was performed [26, 27]. No other congress reports on the use of LMV in primary prophylaxis in high-risk allo-HCT adult patients were found.

Data from 11 studies on primary anti-CMV prophylaxis with LMV were presented or published in 2019. A total number of 401 patients were reported to be administered LMV (Tab. IV).

LTV use in a real-world setting was associated with substantial reduction in CMVi and cs-CMVi without any discernible myelosuppression in all studies in comparison to the cohort group in all studies with the control (usually historical) group. LMV prophylaxis was highly effective at mitigating CMV disease, CMV-related mortality, and the need for toxic CMV therapies. No significant adverse effects with LMV were observed in any study. Discontinuation of LMV was reported in few cases only.

LTV reduced the incidence of cs-CMVi including a trend towards decreased mortality. Patients on LTV prophylaxis had less CMV infections (21% vs 52%, p=0.01), less CMV disease (6% vs 10%, ns), less hospitalization for CMV infection treatment (7% vs 12%, ns), and lower all-cause mortality at day 100 (4% vs 14%, p=0.1) (abstract TCT #396). In multivariate analysis, two factors had an impact on

Table IV. Summary of reported data in abstracts on major hematology/HCT meetings or published in 2019

Study reference	Number of patients	High-risk patients	Beginning of LMV	CMVi rate vs control
Lau et al. (TCT, #127)	10	CMV R+ (CBT)	+7	0% vs 82%
Foolad et al. (TCT, #396)	53	CMV R+		21% vs 52%
Merchant et al. (TCT, #406)	30	CMV R+	+14	20% vs 63%
Dadwal et al. (TCT, #546)	59	Haplo, CBT, ATG	+13	22% vs 41%
Lin et al. (TCT #128; EBMT #405; [27])	53	CMV R+ (TCD, haplo)	+7	5% (no control)
Robin et al. (EBMT, #406)	22	CMV R+		0% (no control)
Derigs et al. (EBMT, #407)	35	CMV R+		14% vs 58%
Kodiyanplakkal et al. (EBMT, #427)	31	CMV R+, ATG, anti-CD52		3% (no control)
Satake et al. (EBMT, #473)	13	Haplo, MUD, MMUD	0	0% (no control)
Karam et al. (ASH, #3269)	63	Haplo, MUD, CBT, ATG		27.6% vs 71%
Sharma et al. [26]	32	CBT (double/haplo), CMV R+	0	0% vs 15%

TCT – Transplantation and Cellular Therapy Meeting; EBMT – European Society for Blood and Transplantation Meeting; ASH – American Society of Hematology Meeting; CMVi – significant cytomegalovirus infection; HCT – hematopoietic cell transplantation; CBT – cord blood transplantation; MUD – matched unrelated donor; MMUD – mismatched unrelated donor; haplo – haploidentical HCT; R+ – seropositive recipient; ATG – anti-thymocyte globulin; ND – no data
Source data:
Abstracts from the 2019 TCT Meetings of ASBMT and CIBMTR, February 20-24, 2019 Houston, Texas. Biology of Blood and Marrow Transplantation 2019; 25(3):A4-S442 (Supplement).
The 45th Annual Meeting of the European Society for Blood and Marrow Transplantation: Physicians. Poster Session. Bone Marrow Transplantation (2019) 54:144–619. https://doi.org/10.1038/s41409-019-0559-4.
61 Annual Meeting of American Society of Hematology. Orlando (December 7-10, 2019). Blood 2019;134 (Supplement 1; November 13 2019):abstract 3269.

occurrence of cs-CMVi at day +100: LMV use decreases the risk, while treatment of GVHD increased it. Notably, the positive impact of LMV was much stronger than the adverse effect of GVHD. The use of LMV was the only factor influencing the risk of occurrence of any detectable CMV viremia. Type of transplantation and donor CMV serostatus had no significant impact on CMV viremia or cs-CMVi infection (abstract TCT #396).

The LTV group had a significant reduction in CMV infection rate: 22.4% vs 41.1% (p=0.008). The high-risk HCT patients had a higher benefit (22.2% vs 62.8%, p=0.004) than the low-risk group (22.8% vs 35.6%, ns) with LTV prophylaxis (abstract TCT#546). The low level CMVi, if any, resolved spontaneously in majority of patients with continued LTV prophylaxis and preemptive treatment was not necessary (abstract TCT#546).

The presented data suggest that CMV infection is considerably inhibited by administration of LMV early after HCT (abstract EBMT #473). LMV prophylaxis resulted in a low rate of CMV infection in high-risk, *in-vivo* TCD allo-HCT population (abstract EBMT #427). The safety and efficacy of LMV for the prophylaxis of CMV reactivation in seropositive patients after allo-HCT was confirmed (abstract EBMT #407).

Primary LTV prophylaxis significantly reduced CMV reactivation, and high-risk patients may benefit from extended prophylaxis. LTV was well tolerated. Additional studies are needed to determine optimal prophylaxis duration in high-risk allo-HCT (abstract TCT #128).

The benefit of LTV prophylaxis is reducing the risk of clinically significant CMV infection in unselected high-risk CMV-seropositive HCT patients, including a substantial number of high-risk transplant recipients. In contrast to the pivotal Phase III study, only a few CMV infections occurred past day 100 after discontinuation of LTV prophylaxis. No significant differences were observed in any other outcome variables including OS, non-relapse mortality, relapse, acute GVHD, or time to neutrophil or platelet recovery (abstract ASH #3269).

LMV is safe and effective compared with alternative prophylaxis approaches following CBT through day 100. No patients in the LMV group received additional CMV-directed treatment while on LMV [26]. LMV was well tolerated in CBT recipients. Data are very promising, and the extent of the benefit suggests that LMV could be a cost-effective new standard of care in adult CBT (abstract TCT #127). Notably, because CMV is known to reactivate early after CBT [28], it is suggested to initiate LMV therapy on transplant day 0. No delays in engraftment or graft failure issues were observed with this approach [26].

A significant potential concern with LMV prophylaxis, particularly following CBT, is the possibility for delayed reactivation and CMV disease following discontinuation of the drug [26]. Until more robust data on this question are available, it was postulated that in patients at high risk for CMV reactivation, the prophylaxis with LMV should be continued. Serial CMV monitoring at least monthly through 6 months post CBT is recommended [26].

As delayed post-prophylaxis CMV reactivation remains a potential concern, the monitoring after day 100 should be mandatory. The duration of needed prophylaxis beyond day +100 requires investigation in CBT recipients (abstract TCT #127) and possibly in patients on immunosuppressive therapy for GVHD. Given its demonstrated benefits, LTV should be considered in all CMV-seropositive allo-HCT recipients (abstract TCT #396).

Practical considerations

What is the current rationale for CMV prophylaxis?

The rationale for prophylaxis is clear. It has been proven that being seropositive is associated with increased mortality. In addition, any CMV replication in the patient, including replication in different organs and in different tissues, has negative impact on OS after HCT. The mortality data (in Phase III study and *post hoc* analysis) showed that both in 24 and 48 weeks after HCT, previous prophylaxis with LMV has decreases in all-cause mortality. This is additional rationale for prophylaxis. This rationale is stronger in the high-risk patients compared to low-risk patients, but in the post hoc analysis, after correction for risk status, it remains significant in both groups.

Will CMV prophylaxis change the clinical practice?

Prevention is a better way of managing the disease than treatment itself. This is of particular major value in case of high efficacy and safety. On the basis of existing data on LMV, both from the Phase III study and on the real-world data, both these conditions are being met. Therefore, prophylaxis is recommended, thus significantly changing current clinical practice.

How should patient be monitored during CMV prophylaxis?

Monitoring should be done, just as in the case of preemptive strategy. Breakthrough infection is still possible, although minimized. Another issue is the compliance of the patient, who is responsible for taking oral drug. Break in prophylaxis might lead to CMV reactivation and development of resistance.

Can LMV be considered for CMV treatment?

At the moment data are limited, and only a few cases are available. There are only uncertainties, such as dose. There are other antiviral drugs, such as acyclovir, where the dose for prophylaxis and dose for therapy are significantly different. Another important issue is that with different doses, the safety profile does not have to be the same. Lastly, the data on possible development of resistance to LMV in case of rapidly replicating CMV are also limited. From the practical point of view, it might be similar to fungal infections: a different drug is used for prophylaxis, and another one should be used to treat the breakthrough infection. On the other hand, it might be the approach for other indications in the future.

What should be done in case of low CMV viremia?

Existing data show that patients with a low level of viremia during LMV prophylaxis cleared the viremia while administration of LMV was not changed.

When prophylaxis should be started and how long it should be used?

In the Phase III study, the rule was that that the drug should be started before day 28. Since both oral and intravenous formulae are available, the early start is always possible, regardless of patient tolerability of oral drug. It is important to start early, as CMV reactivation can occur even within first day after transplantation. As LMV is nontoxic, it could be started before the day of the transplant, what was done in several post-Phase-III studies. However, there are no interaction studies with chemotherapeutic agents used in conditioning; thus, it cannot be used before day 0.

So far, the only datum on the length of time is to use until week 14. It was postulated in several studies that the prophylaxis should be prolonged. To answer this question, there is an ongoing study comparing the rationale of prophylaxis until 6 months. Both safety and efficacy are important issues.

For whom prophylaxis is recommended and for whom preemptive treatment?

For patients at a high-risk of CMV viremia, prophylaxis is recommended. There is no doubt about it, because the gain of LMV use is potentially much higher in high-risk patients, and preventing CMV viremia is beneficial for OS. On the other hand, prophylaxis was also effective and safe in low-risk patients. However, one should remember that only CMV-seropositive patients were included in these studies. Thus, with the current data, patients' CMV seropositivity has already a strong indication for prophylaxis. All other allogeneic transplant recipients should be monitored for CMV viremia and preemptively treated in case of its positivity.

Should LMV prophylaxis be prolonged beyond day +100?

So far only data for up to week 14 are available. There is ongoing study comparing shorter versus longer prophylaxis with LMV. This study will answer the question about safety, efficacy, and rationale for prolonged prophylaxis. It is not obvious, as there are different scenarios with different antivirals.

Acyclovir can be taken safely for a year or so. On the other hand, in case of ganciclovir, the longer the use, the higher the risk of toxicity.

Conclusions

The presented real-world evidence confirms Phase III results of LMV in primary prophylaxis in adult CMV-seropositive recipients of allo-HCT. Observational and retrospective studies showed safety and efficacy of LMV for the prophylaxis of CMV reactivation in seropositive patients after allo-HCT. LMV did not delay time to neutrophil and platelet engraftment in any of the studies. HCT patients with a high-risk of CMV reactivation had most benefit with LTV prophylaxis.

LMV was much highly effective than CMV-guided preemptive therapy in preventing CMV infection and CMV disease [25]. The use of LMV in prophylaxis resulted in an improvement in OS during the first 24 and 48 weeks [25, 29, 30]. LMV had a favorable safety profile, as it does not cause myelotoxicity.

LMV is an important addition to the current strategies for CMV prevention after allo-HCT. Its favorable efficacy and safety profile reopen door for another first-line option for antiviral prophylaxis, similar to CMV surveillance and preemptive therapy, for preventing CMV in allogeneic HCT recipients.

This new prophylaxis strategy in CMV+ patients after HCT results in reduced clinically significant CMV infections, less preemptive treatment and hospitalizations, and impact for lower all-cause mortality. First analyses and opinions suggest a significant cost-effective benefit, particularly in the context of reduced adverse effects, such as GVHD and fungal and bacterial infections. Still, more real-life data are needed to confirm this approach.

The standard of care approach to CMV prevention based on CMV surveillance-guided preemptive therapy is being challenged by the recent approval of LMV for primary prophylaxis. Real-word clinical data show dramatic improvement in the reduction of risk of CMV infection and any CMV viremia in all studies performed so far. LMV is the drug that is breaking the paradigm of preemptive therapy with shift to prophylaxis.

Authors' contributions

JS – the only author.

Conflict of interest

The author has received a lecture fee and participated in meetings organized by MSD.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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