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Clinical impact of Letermovir primary prophylaxis on cytomegalovirus-related complications and survival in hematopoietic cell transplant recipients: Data from a prospective multicenter study in Latin America

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Clinical impact of Letermovir primary prophylaxis on cytomegalovirus-related complications and survival in hematopoietic cell transplant recipients: Data from a prospective multicenter study in Latin America

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REVIVIR study (Registry of Cytomegalovirus Prevention with Letermovir in HCT Patients).

Keywords: letermovir, prophylaxis, cytomegalovirus, hematopoietic cell transplant, survival.

Purpose: To compare the incidence of clinically significant cytomegalovirus infection (CS-CMVi), CMV disease (CMV-d) and CMV-related rehospitalization in patients with allogeneic hematopoietic cell transplant (alloHCT) who received letermovir (LET) primary prophylaxis or were managed with preemptive therapy (PET). We further aimed to identify risk factors for overall mortality at day 200 post-HCT.

Methods: A prospective, observational, multicenter cohort study was conducted at 9 centers in Argentina from October 2020 to September 2025. Adult CMV-seropositive alloHCT recipients were included and followed through day 200 post-HCT. A propensity score (PS) was used to balance baseline covariates. An adjusted conditional multivariate logistic regression analysis including PS was implemented to identify independent risk factors for 200-day overall mortality.

Results: Five hundred and fifty-one patients were included (PET: 346 and LET: 205). CMV seronegative donors, alternative donors, and post-transplant cyclophosphamide administration were compared in PET vs. LET groups: 12.4% vs. 30.7% ($p<0.0001$), 56.9% vs. 87.3% ($p<0.0001$), and 51.7% vs. 80.5% ($p<0.0001$), respectively. High-risk stratification for the development of CMV-d was 88.2% in the PET group compared with 97.1% in the LET group ($p=0.0003$). CS-CMVi, CMV-d, and CMV-related rehospitalization at day 100 post-HCT in the PET vs. LET groups were: 54.3% vs. 7.3% ($p<0.0001$), 7.5% vs. 0% ($p=0.0001$), and 37.9% vs. 10.2% ($p<0.0001$), respectively. Multivariate analysis adjusted for PS identified the following risk factors for mortality: primary graft failure, OR 16.57, 95% CI, 5.23-52.52 ($p<0.0001$), GvHD with high dose of corticosteroids, OR 1.9, 95% CI, 1.19-3.04 ($p=0.007$), and lymphopenia < 300/ mm^3, OR 1.78, 95% CI, 1.10-2.89 ($p=0.019$). LET primary prophylaxis was a protective factor for survival, OR 0.51, 95% CI, 0.29-0.89 ($p=0.018$).

Conclusions: LET primary prophylaxis effectively prevented CMV-related complications, reduced rehospitalizations, and had a benefit on overall survival in seropositive alloHCT recipients.

Introduction

Cytomegalovirus infection (CMVi) remains the most common clinically significant infection after allogeneic hematopoietic cell transplantation (alloHCT), with high morbidity and mortality rates. A randomized controlled trial demonstrated that Letermovir (LET) primary prophylaxis in CMV-seropositive alloHCT recipients through day 100 after transplantation proved effective in reducing CMVi reactivation (r-CMVi), clinically significant infection (CS-CMVi), and end organ disease (CMV-d). Compared with preemptive therapy (PET), patients had lower overall mortality at week 24 [1]. Subsequently, two post hoc analyses of this study showed that patients who received LET had lower overall mortality at week 48 and lower rates of CMV-associated and all-cause rehospitalizations [2,3]. LET extended administration to patients who continue at high risk for CMVi complications through day 200 post-HCT proved to significantly reduce CS-CMVi [4].

Many real-life studies confirm these findings and have shown overall survival benefits in terms of one-year non-relapse mortality, especially in patients at high risk for CMV-d, such as those with T-cell depletion [5-7]. Therefore, LET is currently recommended by ECIL and ASTC guidelines [8,9]. Notwithstanding that, and as a result of its high cost, it is not available in many low- and middle-income countries like those in Latin America.

Several large retrospective studies have shown the clinical benefits of LET. However, to the best of our knowledge, no prospective multicenter studies have been published on risk factors for mortality and the benefit of LET in overall survival.

The main purposes of this research were to compare the incidence of CMV-related complications, such CS-CMVi and CMV-d, as well as the reduction in CMV-related rehospitalization at days 100 and 200 post-HCT between patients receiving LET and those managed with PET. Secondary objectives included identification of risk factors for overall mortality (defined as death for any reason) at day 200 post-HCT, and assessment of the impact of LET on survival.

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Material and methods

Setting, patients, and study design

A prospective, observational, multicenter cohort study was conducted at 9 centers in Argentina from 1 October 2020 to 30 September 2025. All adult patients (≥ 18 years of age) who had undergone a first alloHCT and received primary prophylaxis with LET or were managed with PET were evaluated.

Patients were excluded provided that they were CMV seronegative, or had died before day 10 post-HCT with no r-CMVi or were lost to follow-up.

Demographic, clinical, diagnostic, and outcome variables were evaluated and appropriately defined to avoid inconsistencies, and missing data were not allowed. Follow-up was conducted through day 200 post-HCT or longer in patients who remained at risk for CS-CMVi or CMV-d, by direct patient care in accordance with standardized protocols at each center. Data were obtained from databases of the Infectious Diseases Units, the Hematology Laboratory, and the Virology Laboratory.

Patient data were recorded with RedCap (Research Electronic Data Capture) software, and the study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations [10].

Definitions, diagnosis and prevention modality

CMVi was defined as virus nucleic acid detection in blood, plasma, or another fluid or tissue specimen. CS-CMVi was defined as CMV-d or CMV viremia leading to PET[1]. End-organ disease definition was consistent with that applied by the Working Group of the Cytomegalovirus Drug Development Forum [1,11].

Patients were stratified according to the risk of developing CMV-d. Those presenting one or more of the following factors were classified as high risk: ex vivo T-cell depletion, in vivo T-cell depletion with antithymocyte globulin or alemtuzumab use, prednisone (or equivalent) at a dose of 1 mg or more per kilogram of body weight per day for acute graft-versus-host disease (GvHD) grade II-IV, mismatched related or unrelated

donor, haploidentical donor and cord blood transplant [1]. Allogeneic HCT presenting none of the above factors was considered low risk.

For r-CMVi diagnosis, CMV VL (viral load) was measured in plasma with real-time polymerase chain reaction (RT-PCR). Weekly monitoring started on days -2 to 10 and continued through day 200 post-HCT or beyond in patients considered at risk of late CMV-d. The lower limit of quantification was determined according to the method used at each center.

LET administered orally was started after an undetectable CMV VL within the previous 48 hours. It was indicated from day 0 to 10 after HCT and continued through at least day 100 post-HCT. LET was prescribed according to the availability of the drug at each center. Patients received LET at a standard dose of 480 mg/day, while those on cyclosporine received 240 mg/day.

Patients with a positive RT-PCR result who met the institutional threshold for PET, or had a diagnosis of CMV-d, were initiated on appropriate antiviral therapy with ganciclovir, valganciclovir, or foscarnet according to institutional guidelines at each center, given the lack of consensus on this issue.

LET primary prophylaxis and PET were considered mutually exclusive initial prevention strategies. However, patients receiving LET could subsequently receive antiviral therapy in case of CS-CMVi or CMV-d development after prophylaxis initiation. Therefore, LET was analyzed as the primary prevention strategy, whereas post-baseline antiviral treatment was deemed part of the clinical course.

All patients were administered prophylaxis with acyclovir or valacyclovir and sulphamethoxazole-trimethoprim through at least 1 year post-HCT. They received antifungal prophylaxis through at least day 75 post-HCT according to IDSA and GITMO guidelines [12,13]. Definitions and grading of acute GvHD were consistent with the MAGIC consortium [14].

Sample size

The study sample size was based on both the available prospective cohort and the minimum detectable differences for the main CMV-related outcomes. Assuming a two-sided alpha level of 0.05, 80% statistical power, approximately 200 patients in the LET group and 350 patients in the PET group, the study had sufficient power to detect a 12 percentage point absolute difference in CS-CMVi, with an expected incidence

of 50% in the PET group. For CMV-d, assuming an expected incidence of 8% in the PET group, an 8 percentage point minimum detectable absolute difference was observed.

This was an observational study with non-randomized treatment allocation. Therefore, the sample size calculation was considered descriptive and supportive rather than a formal calculation for randomized trials.

Statistical analysis

Continuous variables were summarized as median and interquartile range or mean and standard deviation, according to their distribution. Categorical variables were summarized as absolute frequencies and percentages. Baseline characteristics were compared between the LET and PET groups using the Mann-Whitney U test for continuous variables and the chi-square test or Fisher exact test for categorical variables, as appropriate.

The primary outcomes included clinically CS-CMVi and CMV-d. The secondary outcome was overall mortality at day 200 post-HCT. They were analyzed according to the treatment strategy defined at baseline or at treatment initiation. LET timing and PET initiation were considered to avoid immortal time bias. CS-CMVi and CMV-d cumulative incidence was estimated with the Kaplan-Meier method.

A multivariate logistic regression model was used to identify risk factors for overall mortality at day 200 post-HCT. Variables with $p < 0.05$ in the univariate analysis were included in the multivariate model.

Since LET primary prophylaxis was not randomly assigned, a propensity score (PS) approach was used to reduce confounding by indication. PS was estimated using multivariate logistic regression, with LET primary prophylaxis as the dependent variable. Only baseline or pre-treatment clinical and transplant-related variables were included in the PS model. Covariates were selected a priori based on clinical relevance and their potential associations with both treatment allocation and mortality. They included patient age, refractory malignancy, matched related donor, haploidentical related donor, T-cell depletion, post-transplant cyclophosphamide (PTCy) administration, CMV seronegative donor and high-risk of CMV-d stratification. Variables reported after treatment initiation were not included in the main adjustment set.

Patients were stratified into PS quintiles. Covariate balance between the LET and PET groups was assessed before and after PS stratification using standardized mean differences with values below 0.10 considered acceptable.

The association between LET primary prophylaxis and overall mortality at day 200 post-HCT was estimated using logistic regression adjusted for PS strata. For CMV-related outcomes, cumulative incidence was interpreted considering death before CMVi or CMV-d as a competing event.

All analyses were performed using Stata software, version 18.0 (StataCorp LLC, College Station, TX, USA). A two-tailed p-value <0.05 was considered statistically significant.

Results

A total of 650 patients were evaluated and 99 were excluded because they failed to meet the eligibility criteria (Figure 1). The total study population consisted of 551 patients: 346 (62.8%) were managed with PET and 205 (37.2%) received LET. Baseline characteristics are described in Table 1. There was a male predominance, with a median age of 43 years, which was higher in the LET group. The most frequent underlying diseases were acute myeloblastic leukemia and acute lymphoblastic leukemia, with a large proportion being in complete remission in both groups, while refractory disease was more common in the LET group. In terms of type of transplant, differences were observed between the cohorts: matched related donors were more frequent in the PET group, whereas most patients in the LET group received an HCT from an alternative donor. Other significant differences included higher PTCy use and CMV-seronegative donors, as well as lower lymphocyte counts at 100 days post-HCT in the LET group. In addition, the median time to granulocyte engraftment was longer in this group.

The characteristics of acute and chronic GvHD are shown in Table 2. There were no differences between the groups in the incidence or severity of acute GvHD, whereas chronic GvHD was less frequent in the LET group. All patients had risk factors for CS-CMVi and CMV-d, as outlined in Table 3. Median risk factors were higher in the LET group, and most patients were stratified as high risk for developing CMV-d.

The outcomes are depicted in Table 4 and Figure 2. Patients in the LET cohort had a significantly lower rate of CS-CMVi, CMV-d and CMV-related rehospitalization than those in the PET cohort. In the latter group more

than one CS-CMVi episode was frequently observed. On the other hand, a larger number of patients in the LET cohort developed CS-CMVi between days 100 and 200 post-HCT (27, 13.2% vs. 4, 1.2%, p<0.0001). Overall mortality at day 200 post-HCT was similar between the groups; in addition, CMV-related mortality was very low, with no deaths reported in the LET group. In the univariate analysis factors associated with mortality are depicted in Table 5.

The results of the multivariate analysis adjusted for PS are shown in Table 6. The independent risk factors for 200-day overall mortality were primary graft failure, high-dose corticosteroid use for acute GvHD, and lymphopenia, whereas LET primary prophylaxis was a protective factor for survival.

Discussion

This study showed that LET primary prophylaxis reduced the incidence of CS-CMVi, CMVd, and CMV-related rehospitalization. It also identified the risk factors for 200-day overall mortality and the role of LET on survival. The major findings of the present study include significant differences in baseline characteristics between the cohorts. Patients in the LET group were older, had a higher rate of refractory disease, had more haploidentical transplants and PTCy use. This finding was consistent with the fact that the health-care insurance system in Argentina does not usually provide LET unless high-risk patients are involved. The randomized study by Marty et al. reported otherwise, with cohorts being readily comparable and only one third being at high risk for developing CMV-d [1]. Thus, the comparison in our study could be biased, though partially, given the study prospective design, where all variables were defined, missing data were not allowed and PS was performed.

Unlike Marty's and many other real-life studies, median time to granulocyte engraftment was longer in the LET group. A delay in hematopoietic recovery has been reported in haploidentical HCT and in those who received PTCy [15,16]. This could explain what was observed in the LET cohort.

A lower proportion of patients in the LET cohort developed chronic GvHD. The same was reported in a study that included Alemtuzumab T-cell-depleted alloHCT recipients; whereas another research revealed opposite findings [17,18]. Chronic GvHD causes long-term morbidity and mortality, as well as a negative impact on health-related quality of life [19,20]. Therefore, GvHD-free/relapse-free survival is crucial in alloHCT patients.

More patients in the LET group received PTCy, which could explain the lower rate of chronic GvHD. This is still a controversial issue, since some studies reported the same rate of chronic GvHD in patients who received PTCy as in those who did not [21,22]. Should LET play a role, this significant finding might be addressed in larger studies.

Most patients in the LET cohort had a high burden of risk factors for CS-CMVi and CMV-d and were mostly at high risk of developing CMV-d. However, the incidence of these complications was low through day 100 post-HCT and no patients developed CMV-d. A meta-analysis of 48 real-life studies in alloHCT adults showed that LET effectively reduced the risk of CMV-related complications and overall and non-related mortality beyond day 200 post-HCT [23]. In addition, LET proved to reduce refractory CMVi [24].

Patients in the LET cohort had a low rate of CMV-related rehospitalization. This is crucial, as hospitalization can lead to clinical complications with a negative impact on patients' quality of life. In addition, most patients receive either ganciclovir or foscarnet, which often have adverse effects. Thus, CS-CMVi and CMV-d significantly increase healthcare costs. In this regard, several studies have shown that LET is a cost-effective strategy [25-27].

Thirteen percent of the patients developed CS-CMVi after LET discontinuation between days 100 and 200 post-HCT. They had lower lymphocyte counts by day 100 post-HCT, had received more transplants from haploidentical donors and more PTCy compared to those in the PET cohort, which could explain this fact [28]. On the other hand, LET impairs T cells and “memory-like” NK-cell reconstitution, which could increase late CS-CMVi and CMV-d [29,30]. Both the randomized clinical trials and some real-life studies showed a high rate of CMV-related complications after discontinuation of LET [1,4,31]. Therefore, identifying patients at high risk for CMV-related complications by day 100 after alloHCT is crucial for considering an extension of LET prophylaxis. In this sense, the REACT study demonstrated that measurement of CMV cell-mediated immunity by ELISPOT can identify patients with low immunity and at risk of developing CS-CMVi [32]. Recently, ELISPOT has also been shown to be a good predictor of CS-CMVi in alloHCT patients receiving LET [33]. Unfortunately, this test is neither available in Argentina nor in most Latin American countries.

The risk factors for 200-day overall mortality were accurately identified by multivariate analysis adjusted for PS, and LET was a protective factor for overall survival. These findings indicate that all CMV-seropositive alloHCT recipients should receive LET for at least 100 days after HCT. In addition, high-risk patients, such as those with high doses of corticosteroids for acute GvHD and lymphopenia, should continue LET for longer periods, at least until these conditions are managed.

Our study has some limitations that should be considered. First, one-year non-relapse and overall mortality were not the study objective, and therefore were not analyzed. On the other hand, our study showed survival benefits at 200 days post-HCT, which should also be considered when prescribing LET. Second, CMV VL threshold for initiating PET was not uniform, as it was chosen according to standardized protocols at each center; however, there is no consensus on CMV VL threshold in the literature. Third, we failed to collect the adverse effects information of the antiviral medications used for PET. This could have been useful to measure the negative impact of this strategy.

The strengths of our study rely on its prospective and multicenter design. Moreover, the real-life data provided for this design may reveal the country scenario and help other countries in Latin America.

In summary, LET primary prophylaxis effectively prevented CMV-related complications, reduced rehospitalizations, and had a benefit on overall survival in seropositive alloHCT recipients. Therefore, strategies should be implemented to facilitate access to this antiviral drug in Latin American countries.

Members of the REVIVIR study: Fabián Herrera, Diego Torres, Noelia Mañez, Hugo Peretti, Manuel Alderete, Ana Laborde, Lucas Tula, María L. Pereyra, Florencia Otermin, Silvina García Rojas, María J. Eusebio, Facundo Arguello, Santiago Adriani, María L. Gonzáles Ibáñez, Julieta Dalmaroni, Rocío Gago, María E. Silva, Claudia Salgueira, Rosana Jordán, Cristina Videla, Lucas H. Olivieri, Martín Cañete, Alan H. Gómez, Vanesa Romano, Marina S. Medina and Martín Rolan.

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Authors' Contribution

Conceptualization: F.H., D.T., R.J. Methodology: F.H., D.T., R.J., J.L.C. Software: D.T. and J.L.C. Formal analysis: D.T. and J.L.C. Investigation: L.T., N.M., F.O., A.L., M.L.P., M.A., H.P., M.J.E., S.G.R., N.L., J.D., F.A., M.E.S., M.L.G.I., R.G., S.A. Writing: original draft preparation: F.H. Writing: review and editing: D.T., R.J. and R.F.C. All authors have read and agreed to the manuscript.

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Data Availability Statement: Data is available from the corresponding author upon request.

Declarations

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and was approved by CEMIC Ethics Committee on 1st October 2020 (Approval number 1474) and by the ethics committees from the different participating institutions. Patient consent was waived by the Ethics Committee according to Data Protection Law 25326, section 7, subsection 2.

Competing of interests

F.H. has received speaker honoraria and/or grants from Merck, Sharp & Dohme (MSD), Takeda, Pfizer, Gilead, TEVA, Biomerieux, and Knight Therapeutics. D.T. has received speaker honoraria and/or grants from Gilead, Knight Therapeutics, MSD, Pfizer, and GlaxoSmithKline. L.T. received speaker honoraria from MSD, Takeda and Knight Therapeutics. M.L.P received speaker honoraria from Takeda. J.D. received speaker honoraria from MSD. R.F.C. serves as a consultant, speaker, or scientific adviser for ADMA Biologics, Janssen, Merck/MSD, Partner Therapeutics, Takeda, Shionogi, AiCuris, Roche/Genentech, Astellas, Adagio Therapeutics, Tether, Oxford Immunotec, Karius, and Ansun Pharmaceuticals. He received research grants paid to his institution from Merck/MSD, Karius, AiCuris, Ansun Pharmaceuticals, Takeda,

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Table 1.
Baseline characteristics

Variables	Total (n=551)	PET (n=346)	LET (n=205)	*p*-value
	n (%)	n (%)	n (%)	
Age – Median (IQR)	43 (31-55)	41 (28-53)	46 (33-60)	**<0.0001**
Male	307 (55.7)	188 (54.3)	119 (58)	0.397
Underlying disease				
Acute myeloid leukemia	183 (33.2)	114 (32.9)	69 (33.7)	0.864
Acute lymphoblastic leukemia	157 (28.5)	106 (30.6)	51 (24.9)	0.147
Myelodysplastic syndrome	55 (10)	31 (9)	24 (11.7)	0.298
Non-Hodgkin lymphoma	33 (6)	22 (6.4)	11 (5.4)	0.635
Hodgkin lymphoma	31 (5.6)	19 (5.5)	12 (5.8)	0.858
Aplastic anemia	31 (5.6)	20 (5.8)	11 (5.4)	0.838
Chronic myeloid leukemia	27 (4.9)	18 (5.2)	9 (4.4)	0.669
Myelofibrosis	20 (3.6)	10 (2.9)	10 (4.9)	0.227
Multiple myeloma	4 (0.7)	0 (0)	4 (1.9)	0.019
Chronic lymphocytic leukemia	1 (0.2)	1 (0.3)	0 (0)	1
Other	9 (1.6)	5 (1.4)	4 (1.9)	0.478
Disease status				
Complete remission	370 (67.2)	241 (69.7)	129 (62.9)	0.082
Partial remission	44 (8)	26 (7.5)	18 (8.8)	0.596
Recent diagnosis	8 (1.5)	6 (1.7)	2 (1)	0.716
Refractory	63 (11.4)	32 (9.2)	31 (15.1)	**0.036**
Relapsed	27 (4.9)	18 (5.2)	9 (4.4)	0.669
Chronic phase	39 (7.1)	22 (6.4)	17 (8.3)	0.392
Type of transplant				
Match-related donor	175 (31.8)	149 (43.1)	26 (12.7)	**<0.0001**
Mismatch-related donor	10 (1.8)	9 (2.6)	1 (0.5)	0.1
Match-unrelated donor	79 (14.3)	42 (12.1)	37 (18)	0.055
Mismatch-unrelated donor	33 (6)	13 (3.8)	20 (9.8)	**0.004**
Haploidentical	254 (46.1)	133 (38.4)	121 (59)	**<0.0001**
Alternative donor	376 (68.2)	197 (56.9)	179 (87.3)	**<0.0001**
Source of stem cells				
Peripheral blood	532 (96.5)	335 (96.8)	197 (96.1)	0.652
Marrow	17 (3.1)	9 (2.6)	8 (3.9)	0.393
Cord	2 (0.4)	2 (0.6)	0 (0)	0.531
Type of conditioning				
Myeloablative	390 (70.8)	252 (72.8)	138 (67.3)	0.168
Non-myeloablative	31 (5.6)	16 (4.6)	15 (7.3)	0.184
Reduced intensity	130 (23.6)	78 (22.5)	52 (25.4)	0.45
T-cell depletion	74 (13.4)	42 (12.1)	32 (15.6)	0.248
Anti-thymocyte globulin	68 (12.3)	40 (11.6)	28 (13.7)	0.469
Alemtuzumab	1 (0.2)	0 (0)	1 (0.5)	0.372
$CD34^{+}$-selection	5 (0.9)	2 (0.6)	3 (1.5)	0.366
PTCy	344 (62.4)	179 (51.7)	165 (80.5)	**<0.0001**
Prophylaxis for GvHD				
Mycophenolate mofetil	329 (59.7)	174 (50.3)	155 (75.6)	**<0.0001**
Cyclosporine	121 (22)	44 (12.7)	77 (37.6)	**<0.0001**
Tacrolimus	430 (78)	301 (87)	129 (62.9)	**<0.0001**
Methotrexate	190 (34.5)	158 (45.7)	32 (15.6)	**<0.0001**
Primary engraftment failure	20 (3.6)	12 (3.5)	8 (3.9)	0.792
Time to engraftment (days after HCT) – Median (IQR)	16 (12-22)	15 (11-20)	18 (14-23)	**<0.0001**

Lymphocyte count at 100 days after HCT (cell/mm^3) – Median (IQR)	843 (502-1458)	1085 (698-1651)	605 (380-930)	**<0.0001**
CMV serostatus				
R+/D+	445 (80.8)	303 (87.6)	142 (69.3)	**<0.0001**
R+/D-	106 (19.2)	43 (12.4)	63 (30.7)	**<0.0001**

Abbreviation: PET, pre-emptive therapy group; LET, Letermovir prophylaxis group; IQR, interquartile range; PTCy, post-transplant cyclophosphamide; HCT, hematopoietic cell transplant; R+/D-, recipient seropositive and donor seronegative; R+/D+, recipient and donor both seropositive. P-values were obtained using the chi-square or Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables. Bold: statistically significant.

Table 2.
Acute and Chronic Graft vs. Host Disease

Variables	Total (n=551)	PET (n=346)	LET (n=205)	*p*-value
	n (%)	n (%)	n (%)	
Acute GvHD	226 (41)	136 (39.3)	90 (43.9)	0.289
Time to onset (days after HCT) – Median (IQR)	37 (26-54)	38 (26-55)	36 (25-51)	0.447
Severity: grade II-IV	169 (30.7)	112 (32.4)	57 (27.8)	0.261
Chronic GvHD	135 (24.5)	115 (33.2)	20 (9.8)	**<0.0001**
Time to onset (days after HCT) – Median (IQR)	153 (110-222)	154 (112-229)	126 (108-195)	0.179
Severity: extensive	93 (16.9)	85 (24.6)	8 (3.9)	**<0.0001**

Abbreviation: PET, pre-emptive therapy group; LET, Letermovir prophylaxis group; IQR, interquartile range; HCT, hematopoietic cell transplant. P-values were obtained using the chi-square or Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables. Bold: statistically significant.

Table 3.
Risk factors for CMV infection and CMV disease

Variables	Total (n=551)	PET (n=346)	LET (n=205)	*p*-value
	n (%)	n (%)	n (%)	
Age > 50 years	200 (36.3)	109 (31.5)	91 (44.4)	**0.002**
CMV R+/D-	106 (19.2)	43 (12.4)	63 (30.7)	**<0.0001**
Acute GvHD	226 (41)	136 (39.3)	90 (43.9)	0.289
High dose corticosteroids use	273 (49.5)	185 (53.5)	88 (42.9)	**0.016**
T-cell depletion	74 (13.4)	42 (12.1)	32 (15.6)	0.248
Haploidentical transplant	254 (46.1)	133 (38.4)	121 (59)	**<0.0001**
Mismatch-HLA donor	43 (7.8)	22 (6.4)	21 (10.2)	0.1
Cord blood transplant	2 (0.4)	2 (0.6)	0 (0)	0.531
Lymphopenia	193 (35)	94 (27.2)	99 (48.3)	**<0.0001**
PTCy	344 (62.4)	179 (51.7)	165 (80.5)	**<0.0001**
Number of risk factors – Median (IQR)	3 (2-4)	2 (2-4)	4 (2-4)	**<0.0001**
High risk for CMV disease	504 (91.5)	305 (88.2)	199 (97.1)	**0.0003**

Abbreviation: PET, pre-emptive therapy group; LET, Letermovir prophylaxis group; CMV R+/D-, recipient seropositive and donor seronegative; GvHD, graft vs. host diseases; PTCy, post-transplant cyclophosphamide; IQR, interquartile range. P-values were obtained using the chi-square or Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables. Bold: statistically significant.

Table 4.
Primary outcomes

Variables	Total (n=551)	PET (n=346)	LET (n=205)	*p*-value
	n (%)	n (%)	n (%)	
CS-CMVi				
At day 100 after HCT	203 (36.8)	188 (54.3)	15 (7.3)	**<0.0001**
At day 200 after HCT	233 (42.3)	192 (55.5)	41 (20)	**<0.0001**
CMV disease				
At day 100 after HCT	26 (4.7)	26 (7.5)	0 (0)	**0.0001**
At day 200 after HCT	34 (6.2)	28 (8.2)	6 (2.9)	**0.0164**
Peak viral load (IU/mL) Median (IQR)	1079 (222-3851)	1069 (211-3665)	1120 (363-4300)	0.94
Peak viral load (copies/mL) Median (IQR)	775 (215-2349)	739 (222-2462)	1016 (184-2278)	0.14
Admission for CS-CMVi				
At day 100 after HCT	152 (27.6)	131 (37.9)	21 (10.2)	**<0.0001**
At day 200 after HCT	167 (30.3)	137 (39.6)	30 (14.6)	**<0.0001**
>1 episode of CS-CMVi	56 (10.2)	48 (13.9)	8 (3.9)	**0.0002**
200-day overall mortality	108 (19.6)	75 (21.7)	33 (16.1)	0.11
CMV-related mortality	5 (0.91)	5 (1.45)	0 (0)	0.163

Abbreviation: PET, pre-emptive therapy group; LET, Letermovir prophylaxis group; CS-CMVi, clinically significant CMV infection; HCT, hematopoietic cell transplant. P-values were obtained using the chi-square or Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables. Bold: statistically significant.

Table 5.
Risk factors for 200-day overall mortality after HCT: univariate analysis

Variables	Alive (n=443)	Dead (n=108)	HR (95% CI)	*p*-value
	n (%)	n (%)		
Age > 50 years	155 (35)	45 (41.7)	1.32 (0.86-2.03)	0.196
Acute myeloid leukemia	144 (32.5)	39 (36.1)	1.17 (0.75-1.82)	0.476
Refractory disease	49 (11.1)	14 (13)	1.19 (0.63-2.26)	0.578
Primary graft failure	4 (0.9)	16 (14.8)	19.08 (5.93-79.63)	**<0.0001**
Haploidentical transplant	198 (44.7)	56 (51.9)	1.33 (0.87-2.03)	0.182
Alternative donor	298 (67.3)	78 (72.2)	1.26 (0.79-2.01)	0.322
Myeloablative conditioning	313 (70.7)	77 (71.3)	1.03 (0.64-1.64)	0.895
Anti-thymocyte globulin	54 (12.2)	14 (13)	1.07 (0.57-2.01)	0.826
PTCy	274 (61.9)	70 (64.8)	1.13 (0.73-1.76)	0.568
aGvHD	175 (39.5)	51 (47.2)	1.37 (0.89-2.09)	0.143
HD corticosteroids use for aGvHD	136 (30.7)	48 (44.4)	1.81 (1.15-2.83)	**0.007**
CMV R+/D-	79 (17.8)	27 (25)	1.53 (0.93-2.52)	0.092
Lymphopenia	140 (31.6)	53 (49.1)	2.09 (1.33-3.27)	**0.001**
Letermovir primary prophylaxis	172 (38.8)	33 (30.6)	0.69 (0.43-1.11)	0.111
>1 episode of CS-CMVi	38 (8.8)	17 (15.7)	1.93 (1.04-3.57)	**0.032**
100-day rehospitalization for CS-CMVi	113 (25.5)	39 (36.1)	1.65 (1.02-2.63)	**0.027**

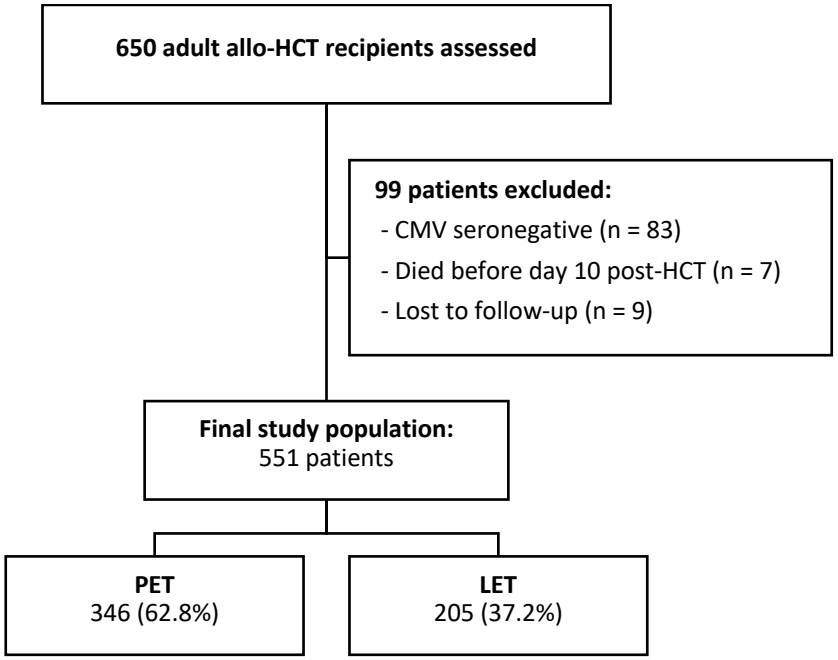
Abbreviation: PTCy, post-transplant cyclophosphamide; aGvHD, acute graft vs. host diseases; HD, high dose; CMV R+/D-, recipient seropositive and donor seronegative; CS-CMVi, clinically significant CMV infection; HCT, hematopoietic cell transplant. P-values were obtained using the chi-square or Fisher's exact test for categorical variables. Bold: statistically significant.

Table 6.
Risk factors for 200-day overall mortality after HCT: multivariable Cox regression with propensity score adjustment

Variables	Multivariable Cox regression		Multivariable Cox regression adjusted for PS	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Primary graft failure	18.78 (5.98-59)	<0.0001	16.57 (5.23-52.52)	**<0.0001**
HD corticosteroids use for aGvHD	1.9 (1.19-3.04)	0.007	1.9 (1.19-3.04)	**0.007**
Lymphopenia	1.87 (1.16-3.02)	0.011	1.78 (1.10-2.89)	**0.019**
>1 episode of CS-CMVi	1.39 (0.69-2.81)	0.359	1.31 (0.64-2.67)	0.454
100-day rehospitalization for CS-CMVi	1.14 (0.66-1.95)	0.641	1.18 (0.68-2.03)	0.552
Letermovir primary prophylaxis	0.59 (0.35-1.01)	0.055	0.51 (0.29-0.89)	**0.018**

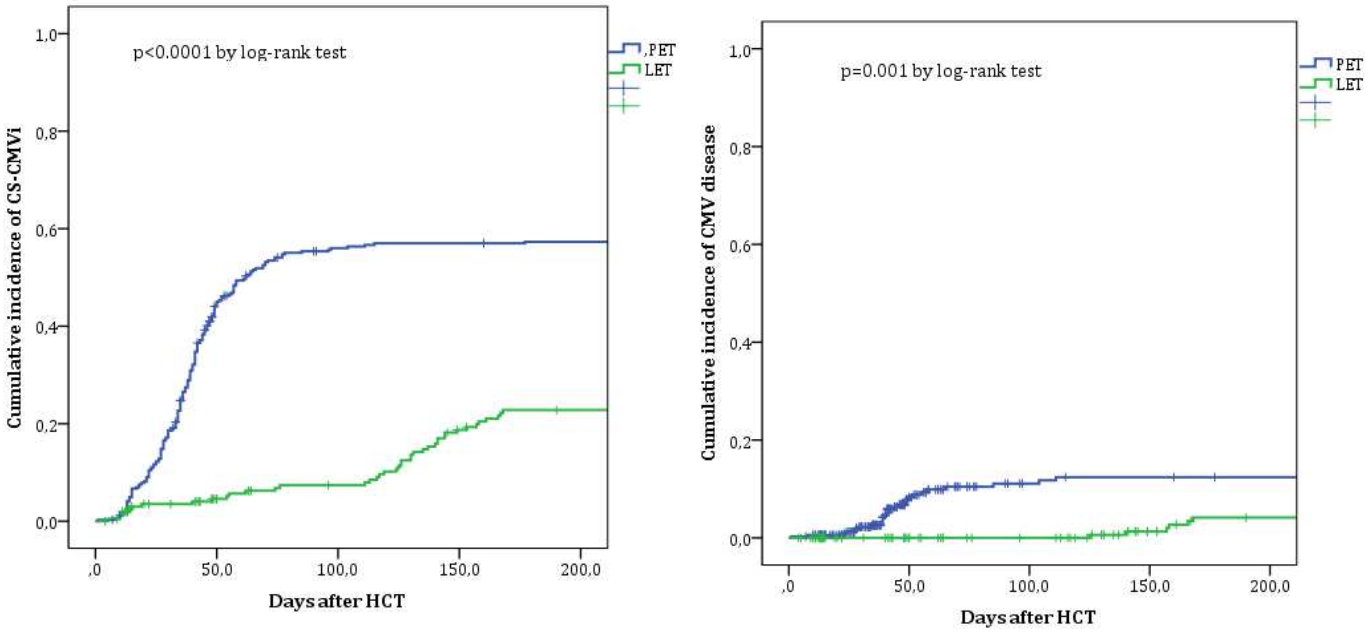
Abbreviation: HCT, hematopoietic cell transplant; PS, propensity score; HD, high dose; aGvHD, acute graft vs. host diseases; CS-CMVi, clinically significant CMV infection. Bold: statistically significant.

Figure 1. Selection of study population



Abbreviation: HCT, hematopoietic cell transplant; PET, pre-emptive therapy group; LET, Letermovir prophylaxis group.

Figure 2. Cumulative incidence curves of Clinically Significant CMV infection (CS-CMVi) and CMV disease



Abbreviation: PET, pre-emptive therapy group (blue line); LET, Letermovir prophylaxis group (green line); CS-CMVi, clinically significant CMV infection.