



Viruses and Viral Diseases

Real-world experience with letermovir for cytomegalovirus-prophylaxis after allogeneic hematopoietic cell transplantation: A multi-centre observational study



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SUMMARY

Objectives: Efficacy and safety of letermovir as prophylaxis for clinically significant cytomegalovirus infections (csCMVi) was evaluated in randomised controlled trials while most of the real-world studies are single-centre experiences.

Methods: We performed a retrospective, multi-centre case-control study at six German university hospitals to evaluate clinical experiences in patients receiving CMV prophylaxis with letermovir (n = 200) compared to controls without CMV prophylaxis (n = 200) during a 48-week follow-up period after allogeneic hematopoietic cell transplantation (aHCT).

Results: The incidence of csCMVi after aHCT was significantly reduced in the letermovir (34%, n = 68) compared to the control group (56%, n = 112; p < 0.001). Letermovir as CMV prophylaxis (OR 0.362) was found to be the only independent variable associated with the prevention of csCMVi. Patients receiving letermovir showed significantly better survival compared to the control group (HR = 1.735, 95% CI: 1.111–2.712; p = 0.014). Of all csCMVi, 46% (n = 31) occurred after discontinuation of letermovir prophylaxis. Severe neutropenia (<500 neutrophils/μL) on the day of the stem cell infusion was the only independent variable for an increased risk of csCMVi after the end of letermovir prophylaxis.

Conclusions: Our study highlights the preventive effects of letermovir on csCMVi after aHCT. A substantial proportion of patients developed a csCMVi after discontinuation of letermovir. In particular, patients with severe neutropenia require specific attention after drug discontinuation.

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Introduction

Clinically significant CMV infections (csCMVi) – including CMV end-organ disease or CMV viremia – can lead to serious complications after allogeneic hematopoietic cell transplantation (aHCT)¹ and are associated with high morbidity and mortality.² They are further associated with graft failure as well as acute and chronic graft-versus-host-disease (GvHD).³ The CMV-seroprevalence rates in the healthy population vary between 40% in industrialised countries and up to 100% in developing countries⁴ – with exceptions such as the Nordic countries, where the seroprevalence is similar to that in southern Europe.⁵ In view of CMV reactivation rates around 80% for CMV-seropositive recipients after aHCT,⁶ effective and tolerable drugs for prevention and treatment of csCMVi are urgently needed. The antiviral agent letermovir was approved by the Food and Drug Administration (FDA) in November 2017 and by the European Medicines Agency (EMA) in January 2018 for prophylaxis of csCMVi in seropositive patients receiving aHCT.⁷

A phase 3, double-blind trial of CMV-seropositive, adult aHCT recipients showed that letermovir prophylaxis resulted in fewer csCMVi compared to placebo.⁸ Frequency and severity of adverse events did not differ between the two groups. In a phase 3 trial with adult CMV-seronegative kidney transplant recipients who received an organ from a CMV-seropositive donor, letermovir was non-inferior to valganciclovir for prophylaxis of csCMVi.⁹ Unlike other anti-CMV drugs, letermovir does not lead to hematologic toxicity or nephrotoxicity.¹⁰ As letermovir targets the viral terminase complex instead of the viral DNA polymerase,¹¹ it retains activity against viruses resistant to other anti-CMV agents.¹² Moreover, naturally-occurring letermovir-resistance is still rare.¹³ Furthermore, current discussions focus on increasing the prophylaxis period from 100 to 200 days, for which the results of a phase 3 trial have already been published (clinicaltrials.gov identifier NCT03930615).¹⁴

The efficacy and safety of letermovir prophylaxis have been tested in randomised controlled trials, but many of the real-world data studies are comparative, single-centre experiences.^{15–18} In this multi-centre study, we examined the efficacy of letermovir as prophylaxis of csCMVi in clinical use for patients receiving aHCT at six German university hospitals. We performed a retrospective case-control study to observe and evaluate clinical experiences with letermovir prophylaxis compared to untreated controls during a 48-week follow-up period after aHCT.

Methods

Study design and study population

We performed a retrospective, multi-centre case-control study at six German university hospitals. In the case group, we included 200 patients who received letermovir as primary CMV prophylaxis after aHCT between January 2018 and December 2020 and compared them with 200 matched control patients that did not receive letermovir prophylaxis. Patients in the control group received their aHCT between January 2016 and December 2017, prior to approval of letermovir in Germany. All patients were followed up for 48 weeks after aHCT or until death. The study was conducted in line with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.¹⁹

Inclusion criteria were first aHCT, 30 days survival after aHCT, 18 years of age or older, documented CMV seropositivity within one year before aHCT, and follow-up data available for 48 weeks after transplant or until death. Furthermore, letermovir patients required absence of CMV viremia from time of transplant to time of receiving letermovir (hence, letermovir prophylaxis). Patients were excluded from the study (i) if they received ganciclovir, valganciclovir, or foscarnet within seven days before transplantation, (ii) if they

received cidofovir, CMV hyperimmune globulin, any investigational CMV antiviral agent or biological therapy within 30 days before transplantation, (iii) if a history of CMV end-organ disease within six months before aHCT existed, and (iv) if evidence of CMV viremia >2000 copies/mL within 30 days prior to transplantation was present.

Control patients were primarily matched to letermovir patients according to (i) age, (ii) CMV risk status according to Marty et al.,⁸ (iii) study centre, and (iv) non-appearance of CMV viremia from the day of aHCT until at least the same day that the matched case group patients received letermovir. If multiple controls were available, secondary matching criteria were (v) closest calendar day of transplant, (vi) gender, and (vii) underlying haematological disease. These matching-criteria reduce the risk of potential bias related to seasonal effects (e.g. higher influenza rates during winter), centre-specific treatment standards, or general advances in medicine due a relatively short study period of a pre-post analysis. For 16 patients of the letermovir group, it was not possible to find control patients at the same study site. Therefore, these patients were matched with control patients at one of the other study sites.

Clinically significant CMV infection (csCMVi) was defined by the onset of CMV end-organ disease or initiation of anti-CMV pre-emptive therapy based on documented CMV viremia.⁸ After the end of letermovir prophylaxis csCMVi was defined by an onset after the completion of CMV prophylaxis with letermovir. Breakthrough infections were defined as csCMVi appearing during CMV prophylaxis with letermovir.

Study objectives and hypotheses

As primary objective, the clinical effectiveness of letermovir in preventing csCMVi compared to a historical cohort with no treatment was assessed during the 48-week follow-up period. Secondary objectives included the incidence and time to onset of csCMVi in the letermovir vs. control group, CMV-free survival and mortality, as well as the treatment duration of letermovir and the incidence and risk factors of csCMVi after the end of letermovir prophylaxis. Assuming the pre-published results of the letermovir phase 3 trial,⁸ a sample size and power calculation based on a 1:1 ratio was carried out before the start of the study.

Data documentation

Data documentation was performed anonymously. All data were retrospectively documented into a web-based eCRF, accessible via www.clinicals-surveys.net, after conclusion of the 48-week observation period or after death of the patient. Documentation was performed by medical documentation specialists under supervision of experienced haematologists at the participating centres. Data monitoring and query management were performed by the leading study site Cologne.

Statistical analysis

The data were processed and analysed using SPSS (version 28.0, IBM Corp., Armonk, NY, USA). Patient characteristics and outcomes were presented as percentages (absolute numbers) for categorical variables and mean (95% confidence interval = 95% CI) for continuous variables. Age and treatment durations were described as median (inter quartile range/range). Statistical significance was shown using the Pearson's chi-square test, Mann-Whitney U Test, log-rank test or student's t-test (two-sided), as appropriate, with $p < 0.05$ as significance level. Logistic regression and Cox regression analyses were performed using maximum likelihood estimation and included independent patient characteristics as well as the use of letermovir as CMV prophylaxis in the analyses. Prior to multivariate

analyses, univariate analyses were performed, and all variables with $p < 0.1$ were included in the model. The multivariate analyses reported odds ratios (OR) for logistic regression or hazard ratios (HR) for Cox regression and 95% CIs; the level of significance was set at $p < 0.05$. Survival analysis was conducted using the Kaplan-Meier method to estimate the cumulative probability of death over time. The Cox Proportional-Hazards Regression model was employed to assess the association of patient characteristics as well as the use of letermovir as CMV prophylaxis with CMV-free survival and overall survival. No sensitivity analyses were carried out.

Results

Study population

We analysed a total of 400 haematological patients with or without letermovir prophylaxis after aHCT ($n = 200$ for each group). Both groups were well matched according to age, gender, body mass index, underlying haematological disease as well as other comorbidities, graft source, CMV status of the donor, and conditioning regimen (Table 1). Significantly more patients in the control group received mycophenolate mofetil than in the case group (63%, $n = 125$ vs. 76%, $n = 151$; $p = 0.005$). With respect to the main study outcomes, no missing data or loss to follow-up data were documented and had no impact on our study results.

Treatment duration and time of hospitalisation

In the case group, letermovir prophylaxis was started a median of nine days after aHCT (IQR 1–17). The median duration of letermovir prophylaxis was 87 days (IQR 74–100). All patients received letermovir orally. The time of the initial hospitalisation with aHCT (36 days, IQR 31–44 vs. 39 days, IQR 33–49; $p = 0.780$) and the overall hospital length of stay within the observation period until week 48 following aHCT (41 days, IQR 33–57 vs. 47 days, IQR 36–67; $p = 0.176$) was similar in the letermovir and the control group. With regard to the number of patients treated in the intensive care unit (5%, $n = 10$ vs. 10%, $n = 20$; $p = 0.057$) as well as with need for mechanical ventilation (2%, $n = 3$ vs. 2%, $n = 3$; $p = 1.0$) during the observation period, no significant differences were detected between both groups.

Effectiveness of letermovir as CMV prophylaxis

Within the 48-week observation period, the incidence of csCMVi after aHCT was significantly reduced in the group of patients receiving letermovir prophylaxis (34%, $n = 68$) compared to control patients (56%, $n = 112$; $p < 0.001$). Thereby, csCMV viremia occurred in 34% ($n = 67$) of the letermovir and 54% ($n = 108$; $p < 0.001$) of the control group, while only 1% ($n = 1$) and 2% ($n = 4$; $p = 0.117$) suffered from a CMV end-organ disease with CMV encephalitis, retinitis, gastritis or enteritis. Until day 100 after aHCT, the incidence of csCMVi was 19% ($n = 38$) in the letermovir group and 52% ($n = 104$; $p < 0.001$) in the control group, respectively. In the letermovir group, the average onset of csCMV viremia at day 94 (95% CI 76–112) after aHCT was significantly later than in the control group at day 38 (95% CI 32–44; $p < 0.001$). If a csCMVi occurred, no off-label anti-CMV therapy with letermovir was observed. Based on the multivariate logistic regression analysis, letermovir as CMV prophylaxis (OR 0.362) was found to be the only independent variable associated with preventive impact on csCMVi (Table 2). Cox-regression analysis showed that the use of letermovir was the only independent variable associated with impact on csCMVi-free survival until week 48 (HR: 0.456; Table 3).

Reduced mortality in patients receiving letermovir prophylaxis

Overall, 21% ($n = 82$) of the patients died within the 48-week observation period with significant less cases of death in the letermovir compared to the control group (16%, $n = 31$ vs. 26%, $n = 51$; $p = 0.014$; Fig. 1). In both groups, csCMVi was responsible for death of one patient: one died due to CMV encephalitis, the other due to CMV pneumonia. Furthermore, csCMVi potentially contributed to death in one case and ten control patients as these patients received active anti-CMV therapy until death. For the other deceased patients in the letermovir and the control group, the leading non-CMV-related causes of death were relapses of haematological diseases ($n = 19$ vs. 23), sepsis/septic shock ($n = 6$ vs. 10), other co-infections ($n = 2$ vs. 3), and other reasons ($n = 2$ vs. 4). The Cox-regression analysis demonstrated that the use of letermovir was the only independent variable with a significantly reduced risk for death within the observation period until week 48 (HR: 0.588, Supplementary Table 1), whereby the occurrence of GvHD $\geq$ grade 2 (HR: 2.263) and severe neutropenia (< 500 neutrophils/ μ L) on day of aHCT (HR: 1.878) were associated with an increased risk for death.

Contributors to increased risk of csCMVi during and after letermovir cessation

Out of 68 patients in the letermovir group who developed csCMVi during the observation period, in 54% of the patients ($n = 37$) csCMVi was diagnosed during letermovir prophylaxis and in 46% of the patients ($n = 31$), it was diagnosed after discontinuation of letermovir prophylaxis. The patient characteristics of these subgroups are shown in Supplementary Table 3. Significantly more patients with csCMVi during letermovir prophylaxis died compared to those with csCMVi after discontinuation ($n = 9$, 24% vs. $n = 2$, 7%; $p = 0.046$). In the subgroup of csCMVi after discontinuation, the median time-point of csCMVi occurrence was 159 days after aHCT (IQR: 129–175 days) and 55 days after discontinuation of letermovir (IQR 34–80). Multivariate logistic regression analysis showed severe neutropenia (< 500 neutrophils/ μ L) on the day of aHCT (OR 2.852) as the only independent variable for an increased risk of csCMVi occurrence after completion of the letermovir prophylaxis (Table 4). With respect to csCMVi occurrence during letermovir prophylaxis, the systemic use of corticosteroids due to GvHD was found to be the only independent variable for increased risk (OR: 2.835, Supplementary Table 2).

Discussion

In our study, we retrospectively analysed the effectiveness of letermovir as CMV prophylaxis in patients receiving aHCT in a multi-centre setting in Germany. We found that the incidence of csCMVi after aHCT as well as the 48-week mortality were significantly reduced in the letermovir compared to the control group. In almost half of the patients of the letermovir group, csCMVi was diagnosed after completion of letermovir prophylaxis.

A phase 3, double-blind trial demonstrated letermovir's positive impact on reducing or preventing csCMVi occurrence in patients initiating prophylaxis in median nine days after aHCT for a median duration of 82 days.⁸ A pivotal phase 3 trial confirmed the efficacy and safety of extending the duration of letermovir prophylaxis from 100 days to 200 days to reduce the incidence of late csCMVi.¹⁴ In our real-world data study, prophylaxis was started nine days after aHCT and lasted a median of 87 days. While 26% of the patients in the mentioned phase 3 trial received letermovir partly intravenously, all our patients were able to take letermovir orally.⁸ Earlier real-world studies already showed the reduced incidence of csCMVi in patients receiving letermovir prophylaxis after aHCT in mainly single-centre study designs,^{15–18,20–23} but only few multi-centre studies exist.^{24,25}

Table 1
Patient characteristics.

	Letermovir group (n = 200)	Control group (n = 200)	p value
Age in years; Median (Range)	60 (18–77)	56 (18–77)	0.081 ^a
Female gender; n (%)	83 (42)	84 (42)	0.919 ^b
Ethnic origin; n (%)			0.467 ^b
– Caucasian	197 (99)	196 (98)	
– Asian	3 (2)	3 (2)	
– Hispanic/Latino	–	1 (1)	
Body mass index; Mean (95% CI)	24.9 (23.7–26.1)	28.9 (23.6–34.3)	0.150 ^c
Primary underlying disease; n (%)			0.512 ^b
– Acute myeloid leukaemia	98 (49)	111 (56)	
– Myelodysplastic syndrome	25 (13)	22 (11)	
– Non-Hodgkin-Lymphoma	22 (11)	14 (7)	
– Acute lymphoblastic leukaemia	19 (10)	17 (9)	
– Chronic myeloid leukaemia	7 (4)	5 (3)	
– Other	29 (15)	31 (16)	
Additional comorbidities; n (%)			0.501 ^b
– Peripheral arterial disease	27 (14)	27 (14)	
– Diabetes mellitus I or II	23 (12)	18 (9)	
– Solid tumour	17 (9)	16 (8)	
– Chronic renal failure	15 (8)	22 (11)	
– Chronic heart failure	14 (7)	21 (11)	
– Chronic pulmonary disease	9 (5)	12 (6)	
Type of aHCT; n (%)			0.103 ^b
– Peripheral blood stem cells	196 (98)	190 (95)	
– Bone marrow	4 (2)	10 (5)	
Positive CMV status of the donor; n (%)	131 (66)	121 (61)	0.300 ^b
Conditioning regimen; n (%)			0.328 ^b
– Myeloablative chemotherapy	132 (66)	149 (75)	
– Reduced-intensity chemotherapy	68 (34)	51 (25)	
– Antithymocyte globulin	59 (29)	59 (29)	
– Monoclonal antibodies	16 (8)	17 (9)	
– TBI ≥12 Gray	10 (5)	6 (3)	
HLA-matching; n (%)			0.082 ^b
– Matched unrelated donor	130 (65)	113 (57)	
– Matched related donor	31 (16)	34 (17)	
– Mismatched unrelated donor	26 (13)	46 (23)	
– Haploidentical transplantation	13 (7)	7 (4)	
Occurrence of acute GvHD grade 1–2 until week 48; n (%)	136 (68)	119 (60)	0.077 ^b
– Skin	74 (37)	65 (33)	
– Gastrointestinal	39 (20)	40 (20)	
– Liver	23 (12)	13 (7)	
– Lung	–	1 (1)	
Occurrence of acute GvHD grade 3–4 until week 48; n (%)	53 (27)	39 (20)	0.096 ^b
– Skin	25 (13)	21 (11)	
– Gastrointestinal	25 (13)	15 (8)	
– Liver	3 (2)	3 (2)	
Additional CMV risk factors; n (%)			0.005 ^b
– Use of systemic corticosteroids ^d due to GvHD	69 (35)	39 (20)	
– HIV positive at day of the stem cell infusion	–	3 (2)	
– Neutropenia (<500 neutrophils/μL) at day of the stem cell infusion	139 (70)	147 (74)	

Abbreviations: aHCT, allogeneic hematopoietic cell transplantation; CI, Confidence interval; CMV, cytomegalovirus; GvHD, graft versus host disease; HLA, human leukocyte antigen; TBI, total body irradiation.

^a Mann-Whitney U-test.

^b Pearson chi-square test (two-tailed).

^c Student t-test.

^d ≥1 mg/kg/day of prednisone or equivalent dose of another corticosteroid.

Our observations highlighted the real-world effects of letermovir in the use of a multi-centre, matched case-control study design. An increased risk of csCMVi is described for patients with acute GvHD requiring corticosteroid treatment due to immunomodulatory effects^{8,26} which could be confirmed in our study. With regard to the influence of letermovir prophylaxis on the mortality after aHCT, the previously published study results differed: The phase 3, double-blind trial study⁸ as well as earlier single-centre, real-world studies^{15,16,22} revealed that the mortality was significantly reduced in patients receiving letermovir prophylaxis compared to control patients. In contrast, other studies – all in a single-centre, real-world study design – observed similar all-cause and non-relapse mortality rates between letermovir and control patients.^{27,28} Our results from a broad cohort of patients after aHCT indicated improved survival when using letermovir as CMV prophylaxis, as we observed a

significantly lower number of all-cause deaths in the letermovir group after 48 weeks. However, it should be noted that only one patient per group died from a csCMVi, but the number of deaths potentially due to csCMVi was lower in the case compared to the control group.

The currently recommended duration of letermovir prophylaxis is 100 days.^{7,8} A single-centre, retrospective analysis in Japan found that 26% (n = 23/81) of patients receiving letermovir prophylaxis after aHCT developed a late-onset csCMVi after day 100 whereby patients with a high CMV risk status were affected more frequently.²⁹ In our cohort, almost half of all patients with csCMVi in the letermovir group developed a csCMVi after the completion of letermovir prophylaxis, meaning 16% (n = 31/200) of all patients of the letermovir group. We could identify severe neutropenia (<500 neutrophils/μL) at the day of the stem cell infusion as the only risk

Table 2

Multivariate logistic regression analyses of independent variables with impact on csCMV replication in blood (viremia) and CMV disease based on patient characteristics and CMV prophylaxis.

Variable	p value (uni-variate)	Odds ratio	95% CI	p value (multi-variate)	Odds ratio	95% CI
Male gender	0.248	1.285	0.839–1.969	-	-	-
Age ≥50 years	0.230	1.344	0.830–2.178	-	-	-
Acute leukaemia as primary underlying disease	0.251	1.289	0.836–1.986	-	-	-
Occurrence of acute GvHD ≥ grade 2	0.886	1.037	0.630–1.708	-	-	-
Use of systemic corticosteroids ^a due to GvHD	0.054	1.690	0.991–2.881	0.033	1.664	1.042–2.657
Positive CMV status of the donor	0.351	1.229	0.797–1.894	-	-	-
Unrelated donor with ≥1 HLA mismatch	0.368	0.765	0.427–1.371	-	-	-
Letermovir as CMV prophylaxis	< 0.001	0.385	0.233–0.550	< 0.001	0.362	0.238–0.550
Myeloablative chemotherapy	0.829	1.057	0.641–1.741	-	-	-
Neutropenia (< 500 neutrophils/μL) at day of the stem cell infusion	0.717	1.098	0.663–1.818	-	-	-

Note: -2 log-likelihood: 524.841; Hosmer-Lemeshow-test: 0.206; Nagelkerkes R²: 0.082; Omnibus chi-square test: < 0.001.

Abbreviations: aHCT, allogeneic hematopoietic cell transplantation; CI, confidence interval; CMV, cytomegalovirus; GvHD, graft versus host disease; HLA, human leukocyte antigen.

^a ≥1 mg/kg/day of prednisone or equivalent dose of another corticosteroid.

Table 3

Cox-regression analysis of independent variables with impact on csCMVi-free survival until week 48.

Variable	p value (uni-variate)	Hazard ratio	95% CI	p value (multi-variate)	Hazard ratio	95% CI
Male gender	0.248	0.835	0.615–1.134	-	-	-
Age ≥50 years	0.220	0.794	0.550–1.147	-	-	-
Acute leukaemia as primary underlying disease	0.786	0.957	0.697–1.314	-	-	-
Occurrence of acute GvHD ≥ grade 2	0.761	0.942	0.640–1.386	-	-	-
Use of systemic corticosteroids ^a due to GvHD	0.154	1.353	0.893–2.050	-	-	-
Positive CMV status of the donor	0.128	0.779	0.565–1.074	-	-	-
Unrelated donor with ≥1 HLA mismatch	0.990	1.003	0.634–1.586	-	-	-
Letermovir as CMV prophylaxis	< 0.001	0.371	0.263–0.523	< 0.001	0.456	0.329–0.631
Myeloablative chemotherapy	0.124	0.758	0.533–1.079	-	-	-
Neutropenia (< 500 neutrophils/μL) at day of the stem cell infusion	0.580	1.110	0.767–1.608	-	-	-

Note: -2 log-likelihood: 1867.862; Omnibus chi-square test: 42.471; Omnibus p-value: < 0.001.

Abbreviations: aHCT, allogeneic hematopoietic cell transplantation; CI, confidence interval; CMV, cytomegalovirus; GvHD, graft versus host disease; HLA, human leukocyte antigen.

^a ≥1 mg/kg/day of prednisone or equivalent dose of another corticosteroid.

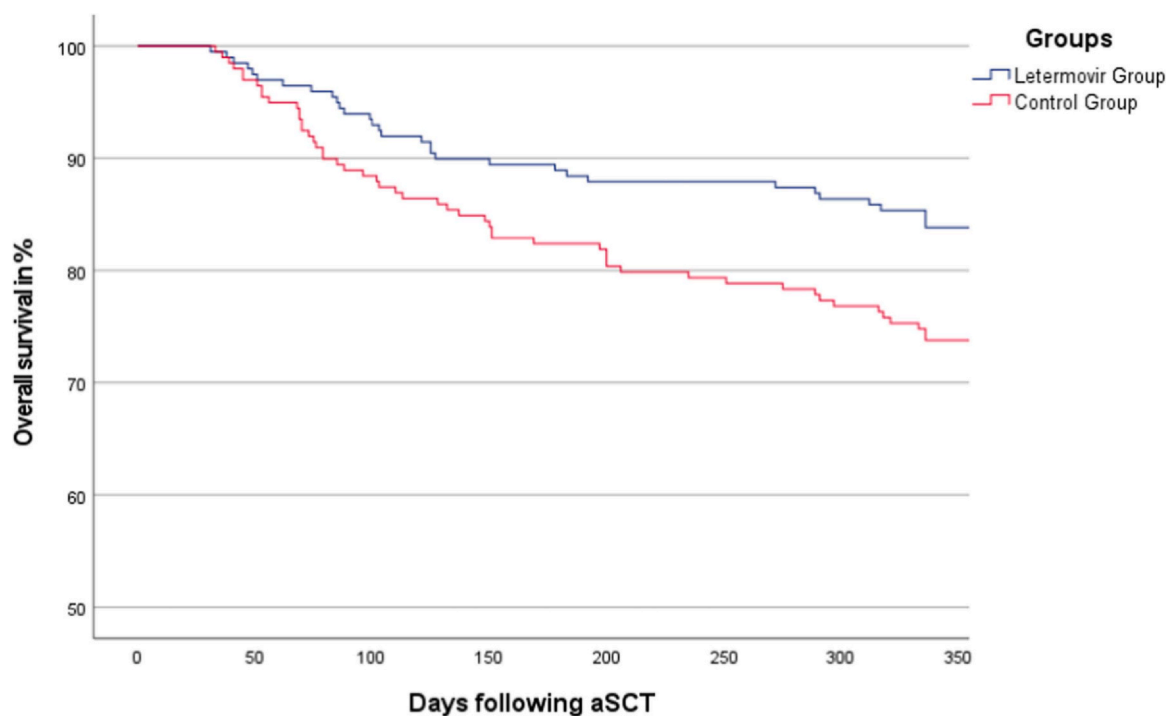


Fig. 1. Overall survival between the observed groups. Kaplan-Meier plot shows overall survival rate (in %) until day 336 (week 48) after allogeneic hematopoietic cell transplantation (aSCT) for the letermovir group (blue line) and the control group (red line; HR = 1.735, 95% CI: 1.111–2.712; log-rank test: $p = 0.014$).

Table 4

Multivariate logistic regression analysis of independent variables of patient characteristics with impact on occurrence of csCMV replication in blood (viremia) and CMV disease after completion of letermovir prophylaxis.

Variable	<i>p</i> value (uni-variate)	Odds ratio	95% CI	<i>p</i> value (multi-variate)	Odds ratio	95% CI
Male gender	0.380	0.694	0.307–1.570	-	-	-
Age ≥50 years	0.322	1.635	0.618–4.324	-	-	-
Acute leukaemia as primary underlying disease	0.752	1.134	0.520–2.471	-	-	-
Occurrence of acute GvHD ≥ grade 2	0.581	1.285	0.527–3.137	-	-	-
Use of systemic corticosteroids ^a due to GvHD	0.111	2.068	0.845–5.058	-	-	-
Positive CMV status of the donor	0.110	1.861	0.869–3.983	-	-	-
Unrelated donor with ≥1 HLA mismatch	0.867	1.102	0.356–3.413	-	-	-
Myeloablative chemotherapy	0.057	2.624	0.971–7.095	0.107	2.157	0.846–5.499
Neutropenia (<500 neutrophils/μL) at day of the stem cell infusion	0.011	3.071	1.291–7.306	0.010	2.852	1.285–6.330

Note: -2 Log-likelihood: 211.039; Hosmer-Lemeshow-test: 0.085; Nagelkerkes R²: 0.042; Omnibus chi-square test: 0.029.

Abbreviations: aHCT; allogeneic hematopoietic cell transplantation; CI; confidence interval; CMV; cytomegalovirus; GvHD; graft versus host disease; HLA; human leukocyte antigen.

^a ≥1 mg/kg/day of prednisone or equivalent dose of another corticosteroid.

factor for csCMVi occurrence after completion of the letermovir prophylaxis. It was known that neutropenia (<500 neutrophils/μL) after the day of the stem cell infusion indicated a risk factor for the development of microbiologically and clinically defined infections.³⁰ Furthermore, leukopenia at the time of detection of CMV viremia was related to lower viral response to pre-emptive therapy and was a significant risk factor for progression from CMV viremia to CMV disease, while these results did not apply to neutropenia.³¹ Interestingly, we were able to show that neutropenia at the day of stem cell infusion led to an increased risk of csCMVi after the end of letermovir prophylaxis in our study cohort. This finding could be due to co-linearity with an unobserved covariate such as leukopenia or lymphopenia. Myeloablative therapy was not a significant risk factor for csCMVi after the end of letermovir prophylaxis, although we observed a trend in that direction. We assume that conditioning by myeloablative therapy and the presence of neutropenia at the time of stem cell infusion are related to each other. Larger study populations might provide significant results in this context. Other factors that were known to increase the risk of CMV infection like HLA-mismatched donors, the occurrence of acute GvHD ≥ grade 2, or the use of systemic corticosteroids (≥1 mg/kg/day) due to GvHD could not be identified as risk factors for a csCMVi after completion of the letermovir prophylaxis in our cohort. In contrast, the use of corticosteroids due to GvHD was a significant risk factor for csCMVi during ongoing CMV prophylaxis with letermovir.

Our study is limited by the fact that we had no data about CMV drug resistances. We were therefore unable to consider the causes of CMV breakthrough infections from this perspective. Additionally, we cannot rule out that other comorbidities outside the scope of the study or temporal trends may have influenced the study results; well-known potential weaknesses of retrospective case-control studies.³² This also includes the fact that significantly more patients in the control group received mycophenolate mofetil than in the letermovir group, which could have an influence on the course of csCMVi.³³ Furthermore, a temporal disparity of one to four years between the aHCT of case and control patients exists. Despite the above-mentioned limitations, the strength of our study is characterised by a multi-centre, matched, real-world cohort, which enabled valid comparisons to be drawn between the observed groups. We were able to confirm results from single-centre, real-world studies that letermovir significantly reduced the prevalence of csCMVi. In addition, our study showed that a substantial proportion of patients developed csCMVi after discontinuation of CMV prophylaxis with letermovir. In particular, patients with severe neutropenia require specific attention after discontinuation of letermovir. Future studies are needed to analyse high-risk patients for csCMVi after the end of letermovir prophylaxis who would potentially benefit from prolonged letermovir prophylaxis.

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Ethical statement

A primary ethics vote was obtained at the Ethics Committee of the Department of Medicine at the University of Cologne on 2020-06-03 (local ethics ID approval 20-1023-NIS), as the University Hospital Cologne was the leading study site. Where necessary, participating study sites received their local ethics votes at the respective ethics commissions.

CRediT authorship contribution statement

SMP: Writing – original draft, Conceptualization, Investigation, Methodology, Formal analysis, Project administration, Funding acquisition. **SMW-H:** Writing – original draft, Conceptualization, Investigation, Methodology, Formal analysis, Project administration, Funding acquisition. **JJV:** Writing – original draft, Conceptualization, Investigation, Methodology, Supervision. **AYC:** Writing – review & editing, Investigation. **I-WB:** Writing – review & editing, Investigation. **GB:** Writing – review & editing, Investigation. **CH:** Writing – review & editing, Investigation. **SK:** Writing – review & editing, Investigation. **OP:** Writing – review & editing, Investigation. **ARR:** Writing – review & editing, Investigation. **TSC:** Writing – review & editing, Investigation. **TST:** Writing – review & editing, Investigation. **DT:** Writing – review & editing, Investigation. **MJGTV:** Writing – review & editing, Investigation. **CW:** Writing – review & editing, Investigation. All authors contributed substantially to the manuscript and agreed to the final submitted version.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: SMP received travel grants from Tillotts. SMW-H has received research and travel grants from Astellas, Merck, and Tillotts; research grants from Basilea, Gilead, and 3M; travel grants from Pfizer, and lecture honoraria from Astellas, Merck, and Tillotts. I-WB participated on an advisory board on infection disease treatment in haematology patients by MSD. GB has received research grants from Novartis, honoraria from BMS, Gilead, Jazz, Novartis, Otsuka, and

travel grants from Gilead and Jazz. SK has received speaker or consulting fees from BMS, Jazz Pharmaceuticals, Novartis Pharma GmbH, AstraZeneca, Janssen Pharmaceutica, GSK, Pentixapharm. OP has no conflicts of interest directly related to this work. OP has received honoraria or travel support from Gilead, Jazz, MSD, Neovii, Novartis, Pfizer and Therakos. He has received research support from Incyte and Priothera. He is member of advisory boards to Equillium Bio, Jazz, Gilead, Novartis, MSD, Omeros, Priothera, Sanofi, Shionogi and SOBI. OP acknowledges the support of José Carreras Leukämie-Stiftung (3R/2019, 23R/2021), Deutsche Krebshilfe (70113519), Deutsche Forschungsgemeinschaft (PE 1450/7-1, PE 1450/9-1, PE 1450/10-1) and Stiftung Charité BIH (BIH_PRO_549, Focus Group Vascular Biomedicine). ARR has received grants from DFG Walter Benjamin-Stipendium, unrelated to this work (no support for the present manuscript). DT has received research grants from Gilead Sciences, speaker or consulting fees from Abbvie, AstraZeneca, Gilead, Jazz, Merck/MSD, Noscendo, Novartis, Octapharma, Pfizer, Sanofi, Takeda, & Tillotts, and travel support from Abbvie, Gilead, Jazz, Medac, & Tillotts. MJGTV has received research grants from 3M, Astellas Pharma, Biontech, DaVolterra, Evonik, Gilead Sciences, Glycom, Immunic, MaaT Pharma, Merck/MSD, Organobalance, Seres Therapeutics, Takeda Pharmaceutical and speaker or consulting fees from Astellas Pharma, Basilea, Bio-Mérieux, DaVolterra, Farmak International Holding GmbH, Ferring, Gilead Sciences, Immunic AG, MaaT Pharma, Merck/MSD, Pfizer, Roche, Organobalance, SocraTec R & D GmbH. SK has received speaker or consulting fees from BMS, Jazz Pharmaceuticals, Novartis Pharma GmbH, AstraZeneca, Janssen Pharmaceutica, GSK, Pentixapharm. CW has received consulting fees or travel support from Takeda, mundipharma and Jazz Pharmaceuticals. JJV received research grants from Merck/MSD, Gilead, Pfizer, Astellas Pharma, Basilea, German Centre for Infection Research (DZIF), German Federal Ministry of Education and Research (BMBF), Deutsches Zentrum für Luft- und Raumfahrt (DLR), University of Bristol, Rigshospitalet Copenhagen, German Network University Medicine, German Cancer Consortium (DKTK), German Federal Ministry of Health (BMG), European Union, speaker fees from Merck / MSD, Gilead, Pfizer, Astellas Pharma, Basilea, German Centre for Infection Research (DZIF), University Hospital Freiburg/ Congress and Communication, Academy for Infectious Medicine, University Manchester, German Society for Infectious Diseases (DGI), Ärztekammer Nordrhein, Ärztekammer Hessen, University Hospital Aachen, Back Bay Strategies, German Society for Internal Medicine (DGIM), Shionogi, Molecular Health, Netzwerk Universitätsmedizin, Janssen, NordForsk, Biontech, APOGEPHA, German Cancer Consortium (DKTK), University Hospital Oldenburg, and meeting and travel support from German Centre for Infection Research (DZIF), University Manchester, German Society for Infectious Diseases (DGI), University Hospital Aachen, German Society for Internal Medicine (DGIM), Netzwerk Universitätsmedizin, German Cancer Consortium (DKTK). AYC, CH, TSc, and TSt have no conflicts of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2024.106220.

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