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Letermovir Prophylaxis for CMV Reactivation in Allogeneic Stem Cell Recipients: A Retrospective Single Center Analysis

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Abstract. *Background/Aim: Cytomegalovirus (CMV) reactivation is one of the most clinically significant complications in allogeneic stem cell recipients and a frequent cause for transplantation related mortality. Letermovir is a newly available and recently approved drug for CMV prophylaxis. In a retrospective single center analysis, we investigated the benefit of letermovir as CMV prophylaxis in allogeneic stem cell recipients. Patients and Methods: We included 48 CMV-seropositive transplant recipients from January 2017 to August 2020 from our department. We compared the rate of CMV reactivation in patients who received letermovir as prophylaxis from day 0 after allogeneic stem cell transplantation (alloSCT) with a control group that did not receive CMV prophylaxis. The primary endpoint was CMV reactivation and was defined as an increase of CMV copies over 1250 Ul/ml in the peripheral blood; secondary endpoints were overall survival (OS) up to 180 days, engraftment and all-cause mortality. Results: We included 21 patients in the control group and 27 patients in the letermovir group. Letermovir treatment led to a significantly reduced incidence of CMV reactivation after alloSCT (33.3% in the letermovir group versus 76.2% in the control group, p<0.001). The OS at day 180 was 80.9% in the control group versus 92.6% in the letermovir group (p<0.05). The median duration of letermovir prophylaxis was 192±104 days. Conclusion: Our results indicate that letermovir prophylaxis is associated with a significant lower risk of CMV reactivation and improved overall survival in CMV-seropositive stem cell recipients. Moreover, a prolonged use of letermovir prophylaxis might be a survival benefit.*

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Cytomegalovirus (CMV) belongs to the family of herpesviruses and is one of the common pathogens apart from Epstein Barr Virus (EBV) that can reactivate after allogeneic hematopoietic stem cell transplantation (alloSCT). It is a frequent cause of transplantation related mortality (TRM) due to life-threatening complications manifesting as multiorgan diseases such as CMV pneumonia, gastroenteritis or retinitis (1-5). Over 60% of seropositive recipients and 10% of seronegative recipients develop a CMV reactivation if they have been transplanted from a seropositive donor. Especially, seropositive recipients who receive grafts from a seronegative donor have the highest risk of a CMV reactivation and therefore a high risk of a poor outcome after alloSCT (6). Thus, the prevention of a CMV disease as well as a CMV reactivation itself is one of the most important challenges in patients after alloSCT. Although ganciclovir and valganciclovir are well known prophylactic treatment possibilities for CMV reactivation in solid-organ transplantation, the use of these drugs in allogeneic stem cell recipients induces severe side effects like myelosuppression which can lead to severe infectious complications. Furthermore, CMV reactivation is also associated with an increased risk of acute graft *versus* host disease (GvHD) resulting in increased mortality (7-9). By contrast, in patients with acute myeloid leukemia, CMV reactivation is associated with a decreased incidence of relapse (10). Taken together, the clinical impact of an asymptomatic CMV reactivation has yet to be clarified.

Recently, the new antiviral drug letermovir has been approved for CMV prophylaxis in hematopoietic stem cell recipients. It inhibits the CMV replication by binding to components of the CMV-terminase complex (11, 12). A phase III study showed that letermovir prophylaxis results in a significantly lower risk of CMV infections and is not associated with toxicity in terms of myelosuppression as well as renal and hepatic dysfunction (13).

In this retrospective single center analysis, we investigated the benefit of letermovir as CMV prophylaxis in allogeneic stem cell recipients. We sought to confirm the efficacy and safety of letermovir and furthermore, the impact on overall survival (OS), all-cause mortality, the risk of relapse and the rate of GvHD.

Patients and Methods

Patients. Forty-eight patients undergoing alloSCT due to hematological malignancies were included between January 2017 and August 2020 at the Department of Internal Medicine III, Hematology/Oncology, Klinikum rechts der Isar, Technical University Munich, Munich, Germany. Only patients that were eligible for CMV prophylaxis (CMV seropositive recipient) were included. Patients receiving a second stem cell transplantation were excluded. Twenty-seven patients received Letermovir as CMV prophylaxis and twenty-one patients were included into the control group that did not receive any CMV prophylaxis. The study was performed according to institutional guidelines. Retrospective analysis of patient data was approved by the local ethics committee. Written informed consent to the clinical treatment and to data analysis was obtained prior allogeneic transplantation from all patients.

CMV monitoring and prophylaxis. Based on the European Conference on Infections in Leukemia (ECIL) recommendations (14), all patients were assessed weekly for CMV reactivation during the first 100 days after alloSCT and longer in patients with persistent T-cell immune-deficiency. CMV-DNA was monitored in peripheral blood samples using real-time quantitative PCR to quantify CMV viral loads. CMV reactivation was defined as an increase of CMV copies over 1,250 UI/ml after alloSCT. All CMV seropositive stem cell recipients received letermovir as CMV reactivation prophylaxis according to the national guidelines. Letermovir was administered orally or intravenous from day 0 after alloSCT up to day 100 or longer if the patients had to take immunosuppressive drugs due to GvHD or if a high risk for CMV reactivation was predicted (CMV seropositive recipient, CMV negative donor). Letermovir use was stopped 100 days after alloSCT or as soon as immunosuppression was discontinued. The dose of letermovir was administered according to the summary of product characteristics. Thus, letermovir was applied at a dose of 480 mg once a day if tacrolimus was used as initial immunosuppressive drug or 240 mg once a day if cyclosporine was used as the initial immunosuppressive drug.

GvHD and infectious prophylaxis and treatment. All patients with an HLA-matched donor received *in vivo* T-cell depletion with anti-thymoglobulin as part of their conditioning regime. All patients with an HLA-mismatch donor or haploidentical donor received standard posttransplant cyclophosphamide. GvHD prophylaxis for all patients consisted of either cyclosporine (CyA) and mycophenolate mofetil (MMF), CyA and a short course of methotrexate (MTX) or tacrolimus (TAC) and MMF. Acute (aGvHD) and chronic GvHD (cGvHD) were diagnosed and graded according to standard criteria (15-17).

All patients received intravenous acyclovir or oral valacyclovir for herpes simplex virus (HSV) prophylaxis and trimethoprim-sulfamethoxazole for pneumocystis jirovecii prophylaxis from the start of conditioning. As fungal prophylaxis, micafungin was applied till leucocyte engraftment (defined as neutrophil >500 G/l), following posaconazole after engraftment. All transfused blood products were filtered and irradiated.

Leukocyte and platelet engraftment. Leucocyte engraftment was defined as neutrophil more than 500 G/l and platelet engraftment was defined as platelets more than 20 G/l.

Endpoints and statistical analysis. The primary end point was the rate of CMV reactivation after alloSCT. Secondary endpoints were OS, all-cause mortality, transplantation related mortality (TRM), relapse incidence (RI), non-relapse mortality (NRM), rate of acute GvHD, leucocyte and platelet engraftment and the incidence of GvHD. Probabilities of OS, TRM, RI, NRM and the rate of acute GvHD were calculated using the Kaplan-Meier method. Leucocyte and platelet engraftment were calculated with the *t*-test for independent samples. Two patient groups were designed to assess the impact of letermovir on all endpoints, for which a subset of patients was selected by matching each letermovir recipient with the best matched control patient, if possible. Matching factors were age at alloSCT, donor type, underlying hematological disease, conditioning regimen and stem cell source. With these matching criteria, 27 letermovir recipients were matched with 21 control patients (Figure 1). Univariate analyses were done using the long rank test for OS and the t test for independent samples. All tests were two-sided. The type I error rate was fixed at 0.05. Statistical analyses were performed with SPSS 27.0 (SPSS Inc, Chicago, IL, USA).

Results

Patient characteristics. Both groups were well balanced with regards to baseline characteristics (Table I). Twenty-one patients were included in the control group and 27 patients in the letermovir group. There was no difference between the control group and the letermovir group in terms of age (p=0.629), sex (p=0.468), underlying disease (p=0.682), stem cell source (p=0.188), HLA matching donor type (p=0.087) or conditioning regimen (p=0.537). The median age in the letermovir group was 55 years *versus* 54 years in the control group. As shown in Table I, there was a significant difference regarding the CMV donor status: 57% patients had a CMV positive donor in the letermovir group *versus* 86% patients in the control group (p=0.025). Consequently, 43% of the patients in the letermovir group and only 14% in the control group were considered to be at high risk of CMV reactivation (p=0.025).

In addition, GVHD prophylaxis with posttransplant cyclophosphamide was significantly more frequently used in the letermovir group than in the control group (30% *vs*. 5%, p=0.029). The incidence of aGvHD was comparable between both groups, but there was a trend to lower rates of grade III-IV aGvHD in the letermovir group compared to the control group (18% *vs*. 29%, p=0.131).

Engraftment. There was no significant difference regarding leucocyte and platelet engraftment between both groups. The median time for leukocyte engraftment was 19 days in the letermovir group (95% CI=17-20, p=0.140) *versus* 20 days in the control group (95% CI=18-23, p=0.140). Moreover, the median time for platelet engraftment was 25 days in the

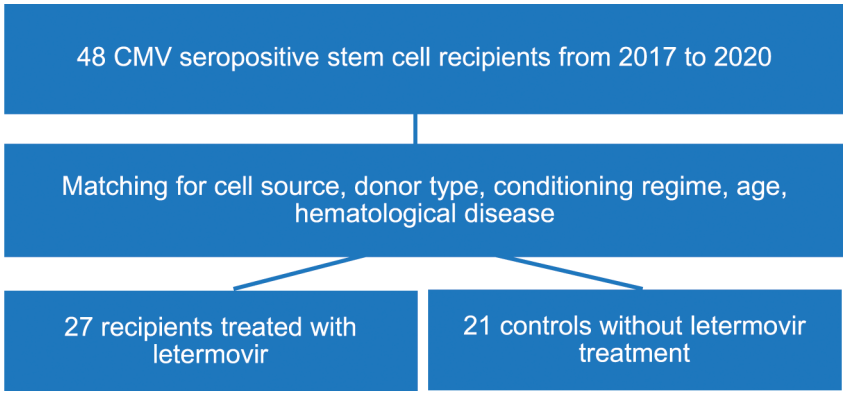

Figure 1. *Flow chart of patient cohort. Patient groups were designed to assess the impact of letermovir. To better compare the differences, two groups were formed. To avoid interfering factors, the groups were matched for cell source, donor type, conditioning regime, age and hematological disease.*

letermovir group (95% CI=16-35, p=0.171) *versus* 27 days in the control group (95% CI=22-23, p=0.171).

Incidence of CMV reactivation. In our patient cohort letermovir treatment led to a significantly reduced incidence of CMV reactivation after alloSCT. Up to day 200, only 33.3% (9 of 27 patients) in the letermovir group developed a CMV reactivation compared to 76.2% (16 of 21 patients) in the control group (p<0.001) (Figure 2A). This beneficial effect was evident in recipients at high risk of CMV reactivation (33.3% in the letermovir group *vs*. 100% in the control group, p<0.001) as well as in recipients at normal risk of CMV reactivation (18.6% in the letermovir group *vs*. 72.2% in the control group, p<0.001) (Figure 2B and C). Thus, letermovir prophylaxis significantly reduced the risk of CMV reactivation in the entire treatment group regardless of the risk profile (Figure 3).

As mentioned above, letermovir was administered according to the summary of product characteristics. Thus, 11 patients in the letermovir group took 240 mg letermovir once a day due to cyclosporine as immunosuppressive drug and 16 patients in the letermovir group took 480 mg once a day due to tacrolimus as immunosuppressive drug.

The median duration of letermovir prophylaxis was 192±104 days in the letermovir group. Six patients had a CMV reactivation after finishing letermovir prophylaxis. The median time to CMV reactivation was 44±17 days after finishing letermovir prophylaxis. Only 3 patients had a CMV reactivation during the use of letermovir. These three patients were severely immunosuppressed due to severe acute GvHD. The median duration of letermovir prophylaxis was 195±118 days in the letermovir group with normal risk for CMV reactivation and 188±87 days with high-risk for CMV reactivation. In the normal-risk group for CMV reactivation only two stem cell recipients had a CMV reactivation (51±33 days after end of letermovir prophylaxis). In the high-risk group for CMV reactivation 4 stem cell recipients suffered a CMV reactivation after finishing letermovir prophylaxis (40±9 days after end of prophylaxis).

Subgroup analysis. The use of letermovir prophylaxis is associated with a significant reduction of CMV reactivations 180 days after alloSCT compared to the control group in the following subgroups: 28.0% *versus* 83.3% among 43 patients receiving PBSC (p<0.001), 22.7% *versus* 81.3% among 38 patients with an unrelated donor (p<0.001), 27.8% *versus* 75% of 38 patients receiving ATG (p<0.001), 25.0% *versus* 100.0% of 9 patients receiving posttransplant cyclophosphamide (p=0.005) and 35.0% *versus* 69.2% of 33 patients who developed an acute GvHD grad II to IV after alloSCT (p=0.001). There was no significant difference regarding the following subgroups due to low numbers of cases: 0% *versus* 40% of 4 patients receiving bone marrow (p=0.515), 50% *versus* 60% of 9 patients with a related donor (p=0.187). Moreover, letermovir prophylaxis decreased the 180-day incidence of CMV reactivation independent of the intensity of conditioning regimens: 23.5% in the letermovir group *versus* 73.3% in the control group among 32 patients receiving RIC (p<0.001) and 33.3% *versus* 83.3% among 15 patients receiving MAC (p=0.002) (data not shown).

We calculated the hazard ratio of the use of letermovir in relation to the incidence of CMV reactivation in different subgroups. As shown in Figure 3, letermovir can significantly reduce CMV reactivations in patients with normal risk for CMV reactivation (HR=0.10, 95% CI=0.02-0.45), unrelated donor (HR=0.25, 95% CI=0.03-2.29), MAC (HR=0.14, 95% CI=0.03-0.58), RIC (HR=0.12, 95% CI=0.03-0.41), ATG use (HR=0.16, 95% CI=0.06-0.45), grades II to IV acute GvHD (HR=0.22, 95% CI=0.08-0.60) and use of PBSC (HR=0.08 95% CI=0.03-0.23).

Table I. *Patient characteristics*.

	Letermovir group (N=27)	Control group (N=21)	*p*-Value
Age (yr)			0.629
Median	55	54	
Range	27-74	29-68	
Male sex - no. (%)	14 (52)	13 (62)	0.468
CMV status donor -no. (%)			0.025
CMV seropositive donor	15 (57)	18 (86)	
CMV seronegative donor	12 (43)	3 (14)	
CMV status stem cell recipient -no. (%)			
CMV seropositive recipient	27 (100)	21 (100)	
Risk of CMV disease - no. (%)			0.025
Normal risk	15 (57)	18 (86)	
High risk	12 (43)	3 (14)	
Primary reason for hematopoetic stem cell transplantation - no (%)			0.682
Acute myeloid leukaemia	16 (59)	8 (38)	
Myelodysplastic syndrome	2 (7)	1 (5)	
Non-Hodgkin's lymphoma	4 (15)	7 (33)	
Myeloproliferative disease	3 (11)	3 (14)	
Acute lymphocytic leukaemia	1 (4)	1 (5)	
Other disease	1 (4)	1 (5)	
Remission status prior to alloSCT (%)		0.363	
Complete remission (CR)	17 (63)	9 (43)	
Partial remission (PR)	4 (15)	4 (19)	
Progressive disease (PD)	6 (22)	8 (38)	
HLA-matching and donor type - no. (%)		0.087	
Matched unrelated	19 (70)	14 (67)	
Matched related	0 (0)	4 (19)	
Mismatched unrelated	4 (15)	2 (10)	
Haploidentical related donor	4 (15)	1 (5)	
Stem cell source - no. (%)			0.188
Peripheral blood	26 (96)	18 (86)	
Bone marrow	1 (4)	3 (14)	
Conditioning regime - no. (%)			0.537
Myeloablative	10 (37)	6 (29)	
Reduced intensity	17 (63)	15 (71)	
Immunosuppressant use - no. (%)		0.104	
Cyclosporine/MMF	10 (37)	14 (67)	
Tacrolimus/MMF	16 (59)	6 (29)	
Cyclosporine/Methotrexate	1 (4)	1 (5)	
Immunosuppressant use - no. (%)		0.029	
ATG	19 (70)	20 (95)	
Post transplant Cyclophosphamide	8 (30)	1 (5)	
Acute GvHD rate- no. (%)			0.131
All grades	23 (85)	14 (67)	
Grade 0	4 (15)	7 (33)	
Grade I-II	18 (67)	8 (38)	
Grade III-IV	5 (18)	6 (29)	

CMV, Cytomegalovirus; no., number; GvHD, graft *versus* host disease; yr, year; alloSCT, allogeneic stem cell transplantation; ATG, anti-thymocyte globuline; MMF, mycophenolate mofetil.

Transplant outcomes. The OS at day 180 was 80.9% in the control group *versus* 92.6% in the letermovir group (p=0.037) (Figure 4A) and consequently significantly better in the letermovir group than in the control group. As shown in Figure 4A, the median OS was not yet reached in the letermovir group whereas the median OS was 380 days (95% CI=88.68-671.32) in the control group.

All-cause mortality at day 180 after stem cell transplantation was 7.4% among letermovir recipients and 19.1% among control group recipients (p=0.037) (Figure 4B).

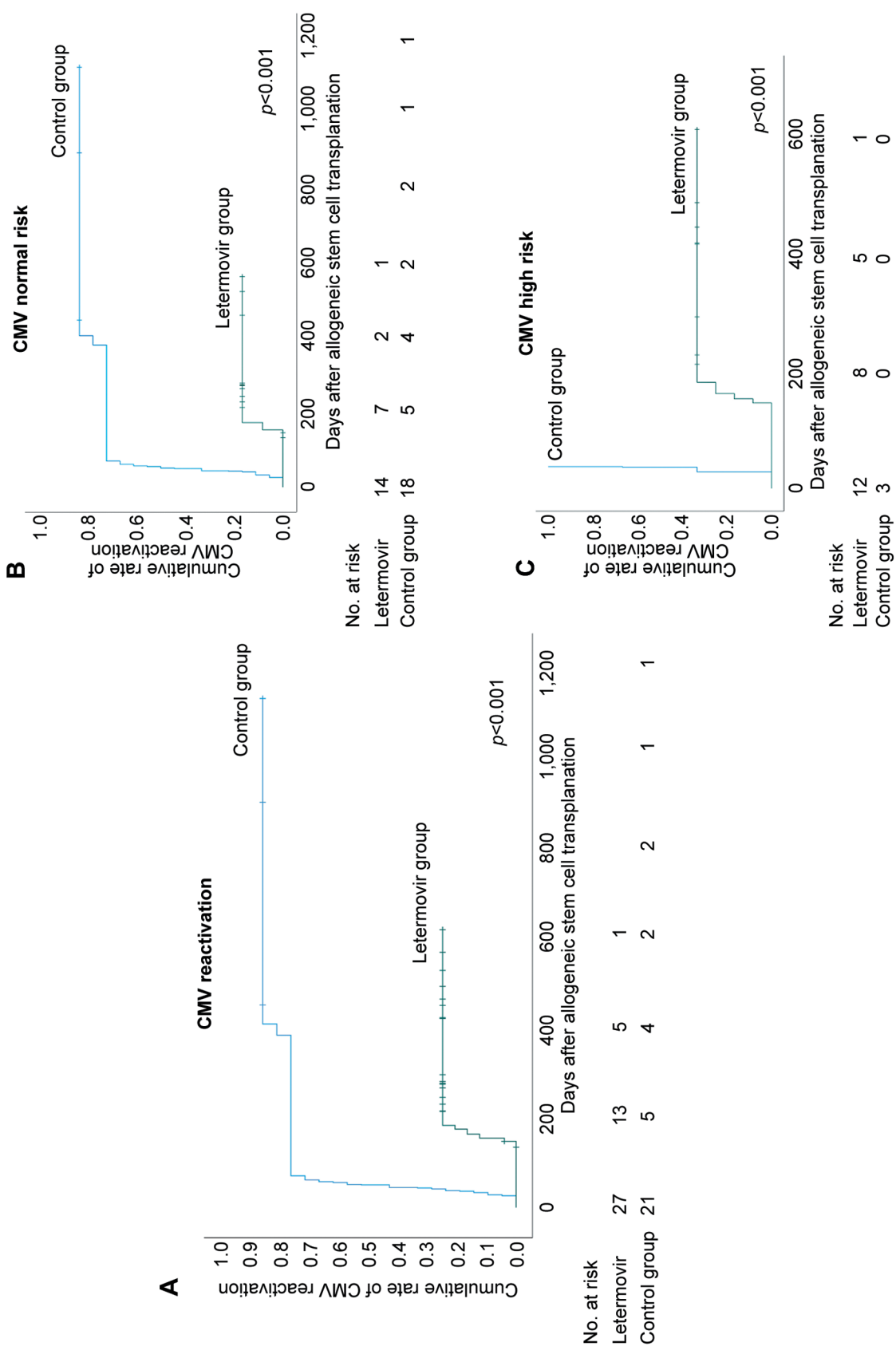

Figure 2. *CMV (cytomegalovirus) reactivation of the entire cohort and of subgroups. (A) CMV reactivation of the entire cohort. Cumulative rate of CMV reactivations through day 500 after allogeneic stem cell transplantation. (B) Rate of CMV reactivation in the CMV normal risk group. Cumulative rate of CMV reactivation through day 500 after allogeneic stem cell transplantation in the normal risk group for CMV reactivation. (C) Rate of CMV reactivation in the CMV high-risk group. Cumulative rate of CMV reactivation through day 500 after allogeneic stem cell transplantation in the high-risk group for CMV reactivation. No., Number.*

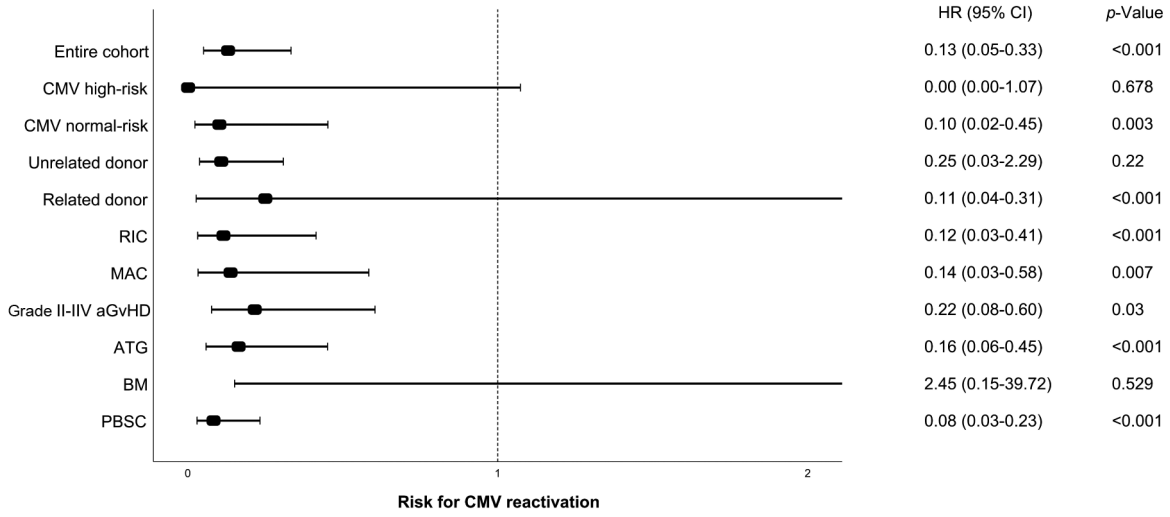

Figure 3. *Forest plots indicating the hazard ratio of letermovir for CMV (cytomegalovirus) reactivation among different subgroups. Letermovir significantly reduces CMV reactivations in nearly all subgroups. No., Number; aGvHD, acute graft versus host disease; RIC, reduced intensity conditioning; MAC, myeloablative conditioning; ATG, anti-thymocyte globuline; BM, bone marrow; PBSC, peripheral blood stem cells; HR, hazard ratio.*

Sixty-seven percent (12 out of 18 recipients) of the patients in entire cohort died due to other reasons than relapse or progression of the original disease whereas 33.3% (6 of 18 recipients) of the patients died due to disease progression or relapse. The main reasons for NRM were sepsis (27.8%) and aGvHD (16.7%). The NRM was significantly higher in the control group with 16.7%, in contrast to the letermovir group with 8.3% at day 180 (p=0.021) (Figure 4C). Regarding the rates of relapse, we did not see a significant difference but there was a trend to lower rates of relapse in the control group than in the letermovir group at day 200 (16.0% *versus* 34.5%, p=0.462) (Figure 4D).

In addition, we monitored the development of aGvHD after alloSCT. There was a trend to lower rates of aGvHD of all grades in the control group, in comparison to the letermovir group at day +100 (53.4% *versus* 66.7%, p=0.102) (Figure 5). There was no difference concerning the rates of aGvHD grad II to IV in both groups (85.7% in the letermovir group *versus* 84.6% in the control group, p=0.642).

Univariate analysis identified a strong association between OS and letermovir prophylaxis (p=0.003). Possible influencing factors like age (p=0.394), sex (p=0.732), mismatched donor (p=0.187), conditioning regime (p=0.395), grade of remission prior to alloSCT (p=0.465) or aGvHD grades II-IV (p=0.064) showed no significant association. By multivariate analysis, the correlation between OS and CMV prophylaxis with letermovir remained significant (p=0.005) independent of the following factors: age ≥ 60 years (p=0.080), type of donor [related *versus* unrelated (p=0.449), matched *versus* mismatched (p=0.104)], immunosuppressant (p=0.372), conditioning regime (p=0.094), risk of CMV reactivation (p=0.113), grade of remission prior to alloSCT (p= 0.342) and aGvHD grades II-IV (p=0.067) (see Table II).

Discussion

In this retrospective analysis a significant reduction of CMV reactivations (76.2% in the control group *versus* 33.3% in the letermovir group, p<0.001) after alloSCT was shown. The risk for CMV reactivation under letermovir prophylaxis was significantly lower independent of the stem cell source (p<0.001), the donor type (p<0.001) as well as the *in vivo* T-cell depletion therapy (p<0.001).

The rate of CMV reactivations in our control group (76.2%) is similar to the results of a recent multicenter retrospective study from Takenaka *et al*. They reported similar rates of CMV reactivation within 100 days after alloSCT when letermovir was not yet available (74.1% CMV reactivation in the first 100 days after alloSCT) (10). This confirms that our control group was representative and comparable and emphasizes the high efficacy of letermovir as CMV prophylaxis with much lower rates of CMV reactivation. Recently, letermovir has also been shown to be safe to use in children and effective in preventing CMV reactivation and associated complications (18). Mori *et al*., in their multicenter retrospective analysis, have seen similar rates of CMV reactivations compared to our retrospective analysis. Moreover, they observed a comparable toxicity profile in terms of leukocyte and platelet engraftment. The median time to leucocyte engraftment in their cohort was 19

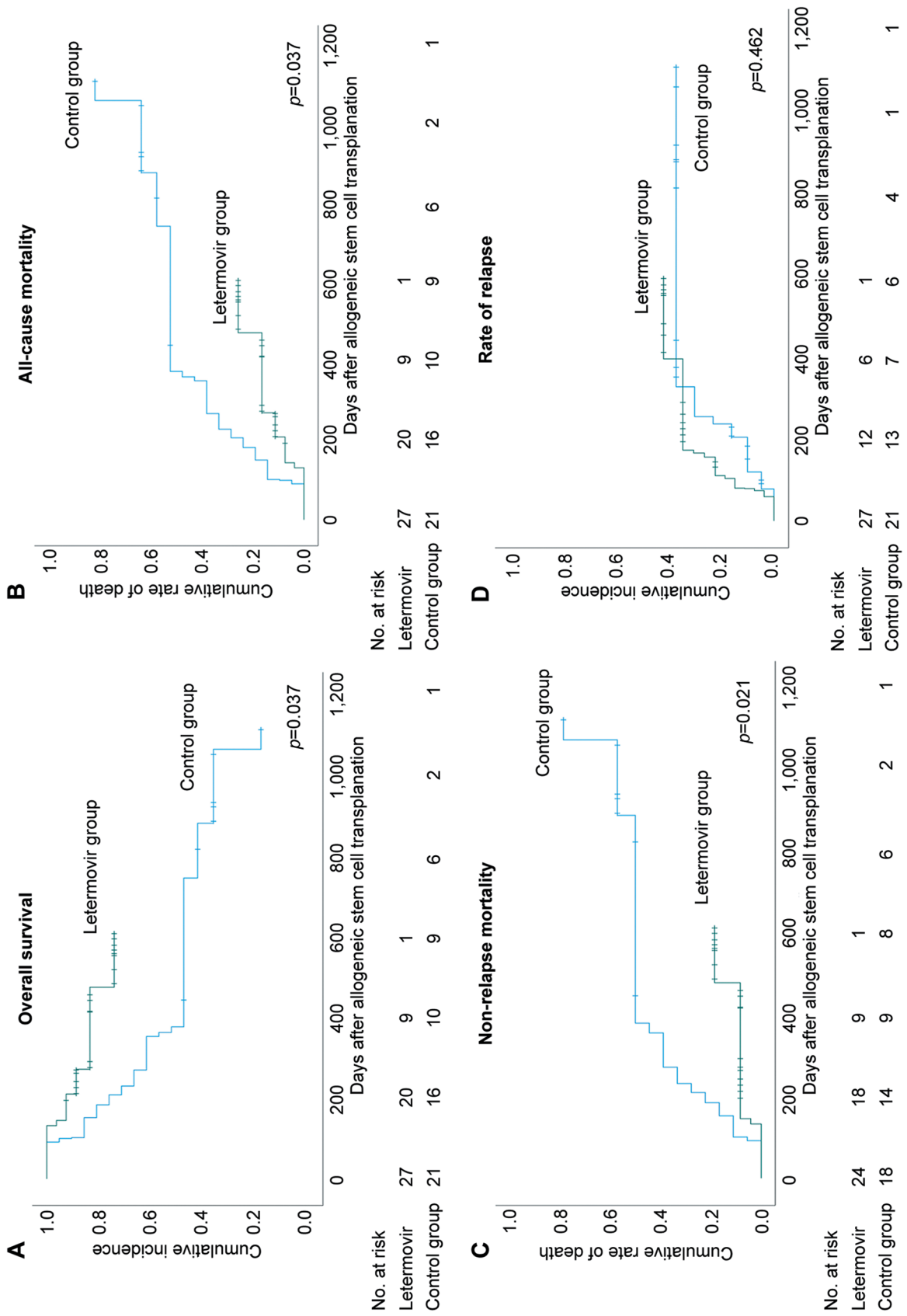

Figure 4. *Survival rates. (A) Overall survival (OS). Stem cell recipients taking letermovir as CMV (cytomegalovirus) prophylaxis have a significant better overall survival than without taking CMV prophylaxis. (B) All-cause mortality. The cumulative rate of death is significantly lower in the letermovir group in comparison to the control group. (C) Non-relapse mortality (NRM). The non-relapsed mortality is significantly lower in the letermovir group in comparison to the control group. (D) Rate of relapse. Letermovir did not lead to higher rates of relapses. No., Number.*

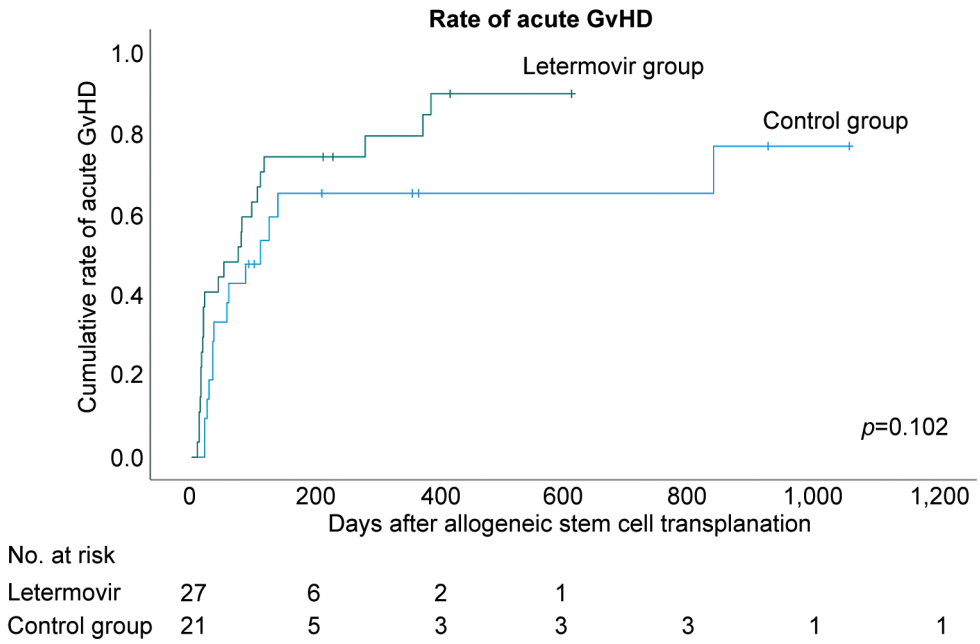

Figure 5. *Rate of aGvHD (acute graft versus host disease) of all grades. Cumulative rate of acute GvHD in the letermovir group and control group. No., Number.*

Table II. *Risk factors for overall survival by logistic regression analysis.*

Characteristics		Univariate		Multivariate	
		Hazard ratio (95% of confidence interval)	*p*-Value	Hazard ratio (95% of confidence interval)	*p*-Value
Age	≥60 *vs.* <60	0.577 (0.1.63-2.042)	0.394		0.080
Sex	Male *vs.* female	0.813 (0.247-2.671)	0.732		0.228
Type of donor	Related *vs.* Unrelated	1.120 (0.242-5.186)	0.885		0.449
Type of donor	Matched *vs.* Mismatched	0.326 (0.062-1.729)	0.187		0.104
Immuno-suppressant use	ATG *vs.* cyclophosphamide	5.565 (0.633-48.965)	0.122		0.372
Conditioning regime	RIC *vs.* MAC	1.711 (0.496-5.905)	0.395		0.094
Acute GvHD (grades II-IV)	Yes *vs.* no	0.216 (0.043-1.093)	0.064		0.067
Letermovir prophylaxis	Yes *vs.* no	0.127 (0.033-0.486)	0.003	0.002 (0.00-0.272)	0.013
Risk of CMV reactivation	High risk *vs.* normal risk	0.487 (0.128-1.848)	0.291		0.113
CR prior to alloSCT	Yes *vs.* No	1.558 (0.474-5.120)	0.465		0.342

CMV, Cytomegalovirus; GvHD, graft versus host disease; ATG, anti-thymocyte globulin; RIC, reduced intensity conditioning; MAC, myeloablative conditioning; CR, complete remission; alloSCT, allogeneic stem cell transplantation.

days in the letermovir group *versus* 17 days in the non letermovir group (p=0.19) and the median time to platelet engraftment was 28 days in the letermovir group *versus* 30 days in the non-letermovir group (p=0.24) compared to 19 *versus* 20 days for leucocyte engraftment (p=0.140) and 25 *versus* 27 days for platelet engraftment (p=0.171) in our cohort (19). Those results prove that letermovir can be safely applied from day 0 after alloSCT without risk of a delayed engraftment and high toxicity rates but with high efficacy of preventing CMV reactivations. These findings on the safety profile of letermovir are consistent with results obtained in several prospective studies of patients with hematopoietic (13) and solid organ transplants (20).

Furthermore, we observed a significantly better OS in the letermovir group compared to the control group (p=0.037) at day 180 after alloSCT. The multivariate analysis confirmed

that letermovir prophylaxis is associated with an improved OS after alloSCT (HR=0.006, p=0.005), independent of established factors like age, type of donor, immunosuppressant use, conditioning regime and acute GvHD grades II-IV. In addition, the NRM was significantly higher in the control group than in the letermovir group (p=0.021). These results are in line with a recently published phase III trial that investigated the effect of letermovir prophylaxis on the mortality of CMV-seropositive recipients after alloSCT (4) as well as other retrospective studies (21, 22). We assume that the reduction of NRM as well as the better OS can be explained by the reduction of CMV reactivations. In the past, it has already been shown that CMV reactivations after alloSCT are associated with increased mortality (23).

Although it is hypothesized that CMV reactivation may lead to lower relapse rates of the original disease, for example, AML, through activation of the immune system (10), our data delineated that the use of letermovir and the hence associated lower CMV reactivation rates, did not lead to an increased relapse rate. Further data is needed to confirm these findings.

Moreover, our analysis tends to slightly lower rates of acute GvHD grad II-IV in the control group with 84.6% than in the letermovir group with 85.7% (p=0.642). This slight trend is in contrast to the published data: On the one hand, CMV reactivations are associated with a higher risk of developing aGvHD due to immunomodulatory effects and on the other hand, aGvHD is associated with high rates of CMV reactivations due to the use of immunosuppressant drugs (22, 24). But this tendency might be due to the small number of patients enrolled in our analysis and might indicate that letermovir does not significantly increase the rate of aGvHD.

Beyond this, our data provide an indication that prolonged use of letermovir leads to significantly lower rates of CMV reactivation and therefore appears to be associated with better OS. The observation that prolonged administration of letermovir beyond day 100 results in lower CMV reactivation rates and CMV disease was also demonstrated in a recently published study (21). Sassine *et al*. described that more than 60% of patients in their letermovir group continued to receive letermovir beyond day 100. The increase in CMV reactivations observed in the phase 3 clinical trial after discontinuation of letermovir at day 100 (13) was also not observed in this study, probably because 60% of their patients receiving primary letermovir prophylaxis received letermovir beyond day 100. However, this needs to be further investigated in a larger study cohort. Nevertheless, longer use (beyond 100 days) appears to be safe and beneficial for patients at risk for CMV reactivation.

Limitations of our analysis are mainly the small numbers of patients as well as the short follow-up period. Furthermore, other limitations of our analysis are the retrospective nature as well as its single-center design. Finally, there was some heterogeneity in both groups of our cohort related to the risk for CMV disease as well as to the GVHD prophylactic regimens and the types of HCT performed owing to changes in clinical practice over time.

In conclusion, we were able to show that letermovir significantly reduces the rate of CMV reactivation after alloSCT and hence, is associated with a significant better OS. Moreover, CMV-prophylaxis with letermovir is well tolerated, especially concerning myelosuppression and GvHD. In addition, our data suggest that prolonged use (more than 100 days after alloSCT) in the setting of clinically increased risk (*e.g.*, prolonged immunosuppression due to GvHD) for CMV reactivation appears to confer a survival advantage for CMV-seropositive stem cell recipients and might be a reason for lower CMV reactivation rates and better OS. However, this assumption needs to be further investigated in a larger study in the future.

Taken together, letermovir is a safe and efficient drug to prevent CMV reactivations in allogeneic stem cell recipients with either normal or high risk of CMV reactivation.

Conflicts of Interest

The Authors have no conflicts of interest to declare.

Authors' Contributions

KK collected data. KK and MV analyzed and interpreted the data. KK, PH, and MV designed the retrospective analysis. FB, KG, LO, IM, and KB provided critical input. KK, PH and MV wrote the manuscript. All Authors critically reviewed and approved the final manuscript.

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