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CORRESPONDENCE

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Increased Epstein–Barr virus reactivation following prophylaxis for cytomegalovirus infection after haploidentical haematopoietic stem cell transplantation

Xin Kong[1,2], Ziyi Xu[1,2], Yanjun Wu[1,2], Xiaowen Tang[1,2], Shengli Xue[1,2], Miao Miao[1,2], Yue Han[1,2], Ying Wang[1,2], Suning Chen[1,2], Aining Sun[1,2], Huiying Qiu[1,2], Depei Wu[1,2], Ye Zhao[1,2] and Feng Chen[1,2*]

Abstract

Letermovir (LTV) prophylaxis is effective in reducing the incidence of clinically significant cytomegalovirus (CMV) infection (cs CMVi) after allogeneic haematopoietic stem cell transplantation (allo-HSCT). Since our centre began administering LTV prophylaxis in June 2022, we have observed a certain increase in the incidence of Epstein–Barr virus (EBV) reactivation after haploidentical HSCT. We retrospectively analysed 230 consecutive patients who underwent haploidentical HSCT with rabbit anti-thymocyte globulin (ATG) from October 2022 to June 2023. The LTV group included 133 patients who received LTV prophylaxis, and the control group included 97 patients who did not receive LTV prophylaxis. At 1 year after HSCT, EBV reactivation was observed in 36 patients (27%) in the LTV group and 13 patients (13%) in the control group ($p=0.012$). All patients with EBV reactivation had EBV-DNAemia, and one patient in each group developed EBV-associated posttransplantation lymphoproliferative disorder (PTLD). The proportion of patients with low EBV-DNA loads ($>5\times10^2$ to $<1\times10^4$ copies/mL) was greater in the LTV group than in the control group (23% vs. 10%, $p=0.01$). The proportion of patients with CMV reactivation was lower in the LTV group than in the control group (35% vs. 56%, $p=0.002$). There was no significant difference between the groups in terms of neutrophil and platelet count recovery, the cumulative incidence of acute/chronic graft-versus-host disease, overall survival, cumulative relapse rate or nonrelapse mortality. Our results show that the increased incidence of EBV reactivation may be associated with LTV prophylaxis for CMV after haploidentical HSCT.

Keywords Hematopoietic stem cell transplantation, Epstein-Barr virus, Cytomegalovirus, Letermovir, Prophylaxis

*Correspondence:
Feng Chen
13584861215@163.com
[1]National Clinical Research Center for Hematologic Diseases, the First Affiliated Hospital of Soochow University, Suzhou 215006, Jiangsu, China
[2]Jiangsu Institute of Hematology, Institute of Blood and Marrow Transplantation, Collaborative Innovation Center of Hematology, Soochow University, Suzhou 215006, Jiangsu, China

To the editor,

Approved for prophylaxis for cytomegalovirus (CMV) reactivation after allogeneic haematopoietic stem cell transplantation (allo-HSCT), letermovir (LTV) has demonstrated a significant decrease in the incidence of clinically significant CMV infection [1]. Following allo-HSCT, Epstein–Barr virus (EBV) reactivation and infection can manifest as a wide range of clinical symptoms, from fever to EBV-associated posttransplantation lymphoproliferative disorder (PTLD) [2–4]. Both CMV and EBV infections lead to significant morbidity and mortality in allo-HSCT recipients [5].

Since our centre began administering LTV prophylaxis in June 2022, we have observed a certain increase in EBV reactivation after haploidentical HSCT. We conducted a retrospective study, approved by the Ethics Committee of the First Affiliated Hospital of Soochow University, that explored the associations of LTV prophylaxis with EBV reactivation in patients after haploidentical HSCT. A detailed description of the methods can be found in Additional file 1.

Findings

A total of 230 patients were included in the retrospective analysis. These patients were divided into LTV ($n=133$) and control ($n=97$) groups on the basis of whether they had received LTV prophylaxis. LTV was administered at a dosage of 480 mg per day (or 240 mg per day for patients on cyclosporine), with prophylaxis starting at a median time of 7 days (range, 028 days) posttransplantation. The CMV-IgM, CMV-DNA and EBV-DNA statuses of the recipient/donor pairs were negative, whereas the CMV-IgG status of the recipient/donor pairs was positive

Table 1 Patient characteristics and clinical results

	Letermovir Group ($n=133$)	Control Group ($n=97$)	*P* Value
Patients			
Men	$n=77$	$n=51$	*0.62*
Women	$n=56$	$n=46$	
Median age (years)	43(12~72)	43(17~65)	*0.36*
Diagnoses			*0.93*
AL	$n=113$	$n=82$	
MDS	$n=20$	$n=15$	
Transplantation			
Disease stage at HCT			*0.14*
Low tumor burden	$n=129$	$n=90$	
Active disease	$n=4$	$n=7$	
Haploidentical Donor	$n=133$	$n=97$	1
Donors sex			*0.35*
Man	$n=97$	$n=76$	
Woman	$n=36$	$n=21$	
Conditioning regimen			*0.01*
Modified BUCY	$n=116$	$n=72$	
others	$n=17$	$n=25$	
rabbit ATG prophylaxis prophylaxis	$n=133$	$n=97$	1
Outcome			
Engraftment			*1*
No engraftment	$n=0$	$n=0$	
Neutrophils (500/μl)	Median day 12 ($n=133$)	Median day 12 ($n=97$)	
Platelets (20 000/μl)	Median day 14 ($n=109$)	Median day 15 ($n=71$)	
aGvHD	$n=16$	$n=15$	*0.76*
I-II	$n=8$	$n=9$	
III-IV	$n=8$	$n=6$	
Relapse[a]	$n=16$	$n=10$	*0.68*
NRM	$n=16$	$n=14$	*0.59*
OS[b]			
1-Year OS	83%	75%	*0.19*

Abbreviations: AL, acute leukemia; BUCY, busulfan cyclophosphamideacute; aGvHD, acute graft versus host disease; HCT, hematopoietic cell transplantation; MDS, myelodysplastic syndrome; NRM, nonrelapse mortality; OS, overall survival. a Time from HCT until relapse. Patients without relapse were censored at the last day of follow-up or on death. b Time between HCT and death of any cause or last follow-up visit

before transplantation. Table 1 presents the clinical characteristics of the study population.

All patients were monitored weekly for CMV and EBV reactivation during the first 3 months after HSCT and then biweekly from 4 to 6 months. The cumulative incidence of EBV reactivation was 23% in the LTV group and 12% in the control group at 100 days post-HSCT and 26% and 12%, respectively, at 24 weeks. At 1 year after HSCT, EBV reactivation occurred in 36 patients (27%) and 13 patients (13%) in the LTV group and control group, respectively. The incidence of EBV reactivation was significantly different between the groups ($\chi^2 = 6.25$, $p=0.012$). All patients with EBV reactivation had EBV-DNAemia, while one patient in each group progressed to PTLD. The Kaplan–Meier event rate of clinical EBV reactivation was 27.7% in the LTV group compared with 14.2% in the control group at one year posttransplantation (log-rank $p=0.023$) (Fig. 1A).

The median time to EBV-DNAemia post-HSCT was 56 days (range, 20 to 204 days) in the LTV group and 52 days (range, 26 to 241 days) in the control group. The EBV-DNA loads varied between the groups. The proportion of patients with low EBV-DNA loads ($>5\times10^2$ to $<1\times10^4$ copies/mL) was significantly greater in the LTV group than in the control group (31 patients (23%) vs. 10 patients (10%); $\chi^2 = 6.47$, $p=0.01$). There was no significant difference in high EBV-DNA load reactivation ($\geq1\times10^4$ copies/mL) between the groups ($\chi^2 = 0.07$, $p=0.78$) (Fig. 1C).

At 1 year post-HSCT, the cumulative relapse rates, nonrelapse mortality rates, and overall survival rates were not significantly different between the LTV and control groups (12% vs. 10%, $p=0.68$; 12% vs. 14%, $p=0.59$; and 83% vs. 75%, $p=0.19$, respectively) (Fig. 1B). Fewer patients in the LTV group than the control group had CMV reactivation, 46 patients (35%) vs. 54 patients (56%), respectively ($\chi^2 = 10.15$, $p<0.002$) (Fig. 1D). Twenty-one patients (17%) in the LTV group and 10 patients (10%) in the control group had concomitant CMV and EBV reactivation, with no significant difference between the groups ($p=0.24$).

Discussion

Our study revealed that for haploidentical HSCT recipients receiving LTV prophylaxis for CMV, the rate of CMV reactivation decreased, whereas the rate of EBV

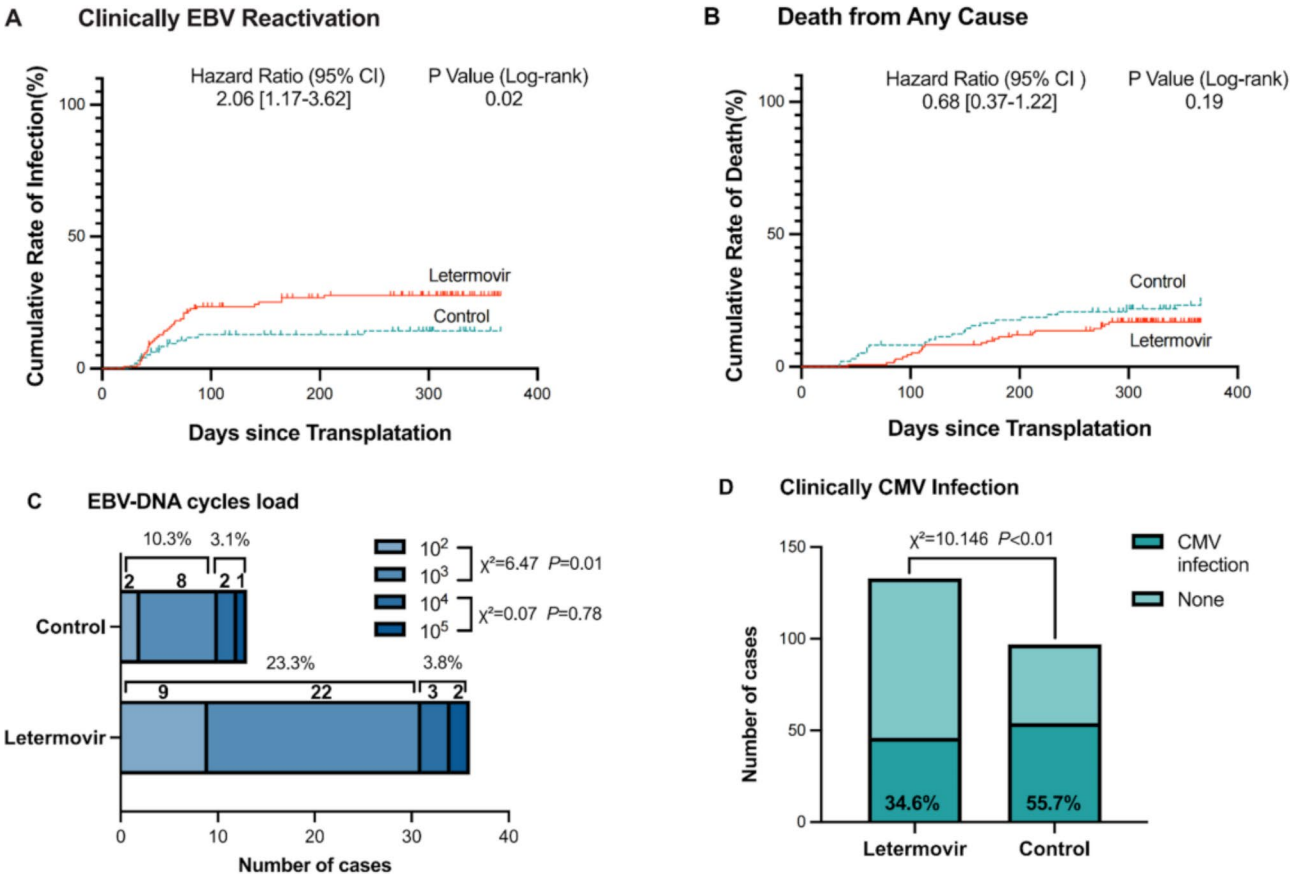

Fig. 1 (**A**) Cumulative rate of clinical EBV reactivation (Letermovir group, solid line; control group, dotted line). (**B**) Cumulative rate of death from any cause (Letermovir group, solid line; control group, dotted line). (**C**) EBV-DNA load in cycles. (**D**) Clinical CMV reactivation

reactivation increased to some extent. Consequently, patients who received LTV prophylaxis had slightly lower all-cause mortality than those who received no prophylaxis through one year after transplantation, with no significant difference ($p=0.68$).

The incidence of EBV reactivation after allo-HSCT ranges from 0.6 to 26%, with higher rates in the context of T-cell depletion [6]. Routine monitoring of EBV-DNAemia via quantitative PCR to identify high-risk PTLD patients, combined with preemptive treatment with rituximab (RTX), has greatly improved the prevention and outcome of PTLD [7]. Considering the adverse effects of a full dose of RTX on B-cell immune reconstitution, 100 mg RTX per week was used in our centre to preemptively treat patients with low-load activation of EBV [8]. In patients whose EBV load did not decrease or increase after low-dose RTX treatment and in patients with high EBV load activation, we administered weekly RTX at 375 mg/m2 and reduced the immunosuppressive therapy intensity as appropriate until EBV-DNAemia resolved. Although the LTV group had a significantly greater incidence of low EBV-DNA load reactivation, there was no progression to a higher EBV-DNA load reactivation or EBV-PTLD.

Most EBV reactivation episodes occurred within the first 6 months post-HSCT, indicating that anti-EBV cytotoxic T lymphocyte-specific responses may take up to 6 months to reconstitute. Gabanti reported delayed immune reconstitution with LTV prophylaxis, achieving the protective threshold of CMV-specific T cells 100 to 120 days later than in the control group, and LTV delayed CMV-specific immune reconstitution, possibly related to decreased CMV antigen exposure [9]. We hypothesize that LTV prophylaxis, while reducing CMV antigen exposure, also leads to a delay in EBV-specific immune reconstitution, perhaps because the two viruses share a common herpesvirus antigen. Further immunologic studies are needed to clarify the reasons for increased EBV reactivation following LTV prophylaxis for CMV.

Abbreviations

LTV	Letermovir
CMV	Cytomegalovirus
HSCT	Hematopoietic stem cell transplantation
EBV	Epstein-Barr Virus
PTLD	Post-transplant lymphoproliferative disorders
RTX	Rituximab

Supplementary Information

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Supplementary Material 1

Author contributions

FC was principal investigator.DW and YZ were senior authors and contributed equally to co-last author.KX and ZX contributed equally, collected data, analyzed and interpreted data.XK wrote the manuscript and created the table and fgure.YW, XT, SX, MM, YH, YW, SC, AS, HQ provided patient care. All the authors agreed to the fnal version of the manuscript.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author(13584861215@163.com) on reasonable request.

Declarations

Ethics approval and consent to participate

The study based on the data from the database of the First Affiliated Hospital of Soochow University, which was established according to the European Society for Blood and Marrow Transplantation (EBMT) registry. The study was approved by the Data Management Committee of the TRUMP and the institutional ethics committee of First Affiliated Hospital of Soochow University (2024 – 367).

Competing interests

The authors declare no competing interests.

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References

1. Francisco M, Per L, Roy C, Johan M, Sanjeet D, Rafael D, et al. Letermovir Prophylaxis for Cytomegalovirus in hematopoietic-cell transplantation. N Engl J Med. 2017;377(25):2433–44.
2. Peric Z, Cahu X, Chevallier P, Brissot E, Malard F, Guillaume T, et al. Features of Epstein-Barr Virus (EBV) reactivation after reduced intensity conditioning allogeneic hematopoietic stem cell transplantation. Leukemia. 2011;25:932–8.
3. Styczynski J, Velden W, Fox CP, Engelhard D, Camara R, Cordonnier C et al. Management of Epstein-Barr Virus infections and post-transplant lymphoproliferative disorders in patients after allogeneic hematopoietic stem cell transplantation: Sixth European Conference on Infections in Leukemia (ECIL-6) guidelines. Haematologica. 2016;101:803 – 11.
4. Patriarca F, Medeot M, Isola M, Battista ML, Sperotto A, Pipan C, et al. Prognostic factors and outcome of Epstein-Barr virus DNAemia in high-risk recipients of allogeneic stem cell pre-emptive rituximab treatment for Epstein–Barr virus reactivation after allogeneic transplantation treated with preemptive rituximab. Transpl Infect Dis. 2013;15:259–67.
5. Heslop HE. How I treat EBV lymphoproliferation. Blood. 2009;114:4002–8.
6. Wagner HJ, Cheng YC, Huls MH, Gee AP, Kuehnle I, Krance RA, et al. Prompt versus preemptive intervention for EBV lymphoproliferative disease. Blood. 2004;103:3979–81.
7. Nicolas S, Myriam L, Inès B, Olivier P, Agnès B, Florent M, et al. Pre-emptive rituximab treatment for Epstein-Barr virus reactivation after allogeneic hematopoietic stem cell transplantation is a worthwhile strategy in high-risk recipients: a comparative study for immune recovery and clinical outcomes. Bone Marrow Transpl. 2020;55(3):586–94.
8. Chen F, Depei W, Tao T, Gong W, Chunmei Y, Xiaowen T et al. Weekly Low-Dose Rituximab as the Preemptive Management of Epstein-Barr Virus Reactivation after Allogeneic hematopoietic stem cell transplantation: a Novel Strategy?[J].Blood, 2015, 126(23):3158–3158.
9. Elisa G, Oscar B, Anna C, Federica Z, Luana B, Daniela C et al. Human Cytomegalovirus-Specific T-Cell Reconstitution and Late-Onset Cytomegalovirus Infection in Hematopoietic Stem Cell Transplantation Recipients following Letermovir Prophylaxis. Transplantation and Cellular Therapy 28 (2022) 211. e1-211.e9.

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