Real-world utilization pattern of letermovir in adult cytomegalovirus seropositive allogeneic hematopoietic stem cell transplant recipients: A multicenter retrospective cohort study from the European Society for Blood and Marrow Transplantation (EBMT) registry

Jan Styczynski[1]; Gloria Tridello[2]; Nina Knelange[3]; Lotus Wendel[3]; Alienor Xhaard[4]; Ilaria Cutini[5]; Patrizia Chiusolo[6]; Georg-Nikolaus Franke[7]; Sabrina Kraus[8]; Amit Raval[9]; Sanjay Merchant[9]; Rafael de la Camara[10]

[1]University Hospital, Collegium Medicum UMK, Bydgoszcz, Poland; [2]Azienda Ospedaliera Universitaria Integrata, Verona, Italy; [3]The EBMT, Leiden Study Unit, Leiden, Netherlands; [4]Hopital St. Louis, Paris, France; [5]Cellular Therapy and Transfusional Medicine Department, Azienda Ospedaliera Universitaria Careggi, Firenze, Italy; [6]Sezione di Ematologia, Dipartimento di Scienze Radiologiche ed Ematologiche, Università Cattolica del Sacro Cuore, Roma, Italy; [7]Medical Clinic and Policinic 1, Leipzig, Germany; [8]Department of Internal Medicine II, University Hospital of Würzburg, Würzburg, Germany; [9]Merck & Co., Inc., Rahway, NJ, USA; [10]Hospital de la Princesa, Madrid, Spain

Background

- Cytomegalovirus (CMV) is a leading opportunistic infection in allogeneic hematopoietic stem cell transplant (HCT) recipients, contributing to substantial morbidity and mortality.[1] Letermovir (LET) was approved by the United States Food and Drug Administration in November 2017 and European Medicines Agency in January 2018 for the prophylaxis of CMV infection and disease in adult CMV-seropositive (R+) recipients of an allogeneic HCT. The LET Phase 3 randomized clinical trial (RCT)[2] demonstrated lower rates of CMV infection, disease, and all-cause mortality among LET-treated participants at week 24. While RCTs demonstrate causal effects between treatments and outcomes, real-world (RW) data answer practical aspects of utilization, such as time to initiation of LET and duration of use
- The objective of this study was to assess LET RW utilization patterns in adult CMV R+ recipients of allogeneic HCT in a large cohort of multiple centers in Europe participating in the European Society of Blood and Marrow Transplantation (EBMT) registry

Methods

- A retrospective observational cohort design was used to examine the RW utilization patterns of LET among CMV R+ recipients of allogeneic HCT in France, Germany, and Italy utilizing data from the EBMT registry. In this registry, members of the EBMT store data that contains information on HCT recipient transplant characteristics and immunosuppressive regimens at the time of transplant (Day 0), 100 days post-transplant, and annually
- Inclusion criteria were CMV R+ recipients, >18 years, who received LET for any reason between January 1, 2018, and December 31, 2020, and had data available for at least 100 days post-allogeneic HCT
- Exclusion criteria were multiple donors, HCT recipients with negative (R-) or unknown CMV serostatus at transplantation, and participation in a clinical trial of any CMV antiviral

Results

- The data presented are a part of the interim real-world utilization data from 5 centers in France, Germany, and Italy. One hundred thirty-eight patients were included
- Median age of patients was 55 years, and 52.2% were males (**Table 1**)
- A majority of donors (64.5%) were unrelated to the patient. Donor/recipient CMV serostatus was 63.8% D+/R+. Stem cell source was mostly peripheral blood (88.4%). T-cell depletion was almost equally split (**Table 2**)
- All centers followed WHO standardization guidelines for CMV viral load assay by PCR. Viral load was determined at the time of LET initiation in 86.2% patients. For 79 cases, the viral load was 0 IU/mL. For the other 5 cases, the mean viral load at the time of initiation was 2.94 IU/ml with a standard deviation of 13.62 IU/mL
- Oral (PO)-only LET formulation was used in 98% of patients (median 2 days post-HCT; letermovir was initiated prior to HCT in 3% of the recipients). Centers indicated that intravenous (IV) formulation was administered only if patients could not tolerate oral. The median duration of PO use was 98 days. Letermovir dose was 240 mg (86%), mostly in patients receiving cyclosporine; 480 mg (9%); or sequentially 240/480 mg (5%) (**Table 4**)

Table 1. Demographic/clinical characteristics of patients (N=138)

Median age at transplant in years (min-max)	55 (19-72)
Gender male, n (%)	72 (52.2)
Diagnosis, n (%)	
Acute leukemia	70 (50.7)
Myelodysplastic/myeloproliferative	40 (29.0)
Lymphoma	15 (10.9)
Others	13 (9.4)

Table 2. Transplant characteristics

Type of donor, n (%)	
Identical sibling	21 (15.2)
Mismatched relative	27 (19.6)
Unrelated	89 (64.5)
Unknown	1 (0.7)
Donor/recipient CMV serostatus, n (%)	
D+/R+	88 (63.8)
D-/R+	50 (36.2)
Other characteristics	
Conditioning regimen, n (%)	
Standard	72 (52.2)
Reduced intensity	57 (41.3)
Unknown	9 (6.5)
Stem cell source	
Peripheral blood	122 (88.4)
Bone marrow	12 (8.7)
Cord blood	3 (2.2)
Unknown	1 (0.7)
T-cell depletion	
No	71 (51.4)
Yes	66 (47.8)
Unknown	1 (0.7)

D+, donor positive; D-, donor negative; R+, recipient positive

Table 3. Center-related details

Centers following WHO standardization guidelines for CMV viral load, n (%)	138 (100)
Measurement of CMV viral load at the time of LET initiation, n (%)	
Yes	119 (86.2)
No	19 (13.8)

Table 4. LET utilization

Formulation used	
Oral only	135 (97.8)
Both oral and IV	2 (1.4)
IV only	1 (0.7)
LET dosage used, n (%)	
240 mg	119 (86.2)
480 mg	12 (8.7)
Both 240 and 480 mg (sequentially)	7 (5.1)
Use of cyclosporine at the time of LET initiation, n (%)	
Yes	119 (86.2)
No	19 (13.8)
Median duration of oral LET in days (range)	98 (10-209)
Median days between transplant and start of oral LET (range)	2 (-3, 20)

Conclusions

Some differences were observed in this interim LET RW utilization analysis compared to the phase 3 RCT. Notably, patients began LET at a median of D+2 post-HCT (compared to D+9 in the trial), and 97.8% received only PO LET (as compared to 26.5% receiving IV LET in the trial). Further studies are needed to determine drivers of LET utilization in RW settings.

References:

1. Jakharia N, et al. *Curr Treat Options Infect Dis.* 2021;13(3):123-140.
2. Marty FM, et al. *N Engl J Med.* 2017;377(25):2433-2444.

https://bit.ly/3dBxvln

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