RESEARCH ARTICLE

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Real-Life Data on the Efficacy and Safety of Letermovir for Primary Prophylaxis of Cytomegalovirus in Allogeneic Hematopoietic Stem Cell Recipients: A Single-Center Analysis

Allojenik Hematopoetik Kök Hücre Alıcılarında Sitomegalovirüsün Primer Profilaksisi için Letermovirin Etkililiği ve Güvenirliğine İlişkin Gerçek Yaşam Verileri: Tek Merkezli Bir Analiz

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Abstract

Objective: Cytomegalovirus (CMV) reactivation is a life-threatening complication after allogeneic hematopoietic stem cell transplantation (HSCT). Introduction of letermovir (LMV) seems to improve post-transplant outcomes, but delayed-onset CMV reactivation still remains a challenge. In this study, we report on our first experience with LMV prophylaxis in 93 CMV-seropositive adult patients receiving HSCT in our center.

Materials and Methods: We retrospectively analyzed the data of 93 adult CMV-seropositive recipients receiving LMV as CMV prophylaxis after HSCT for hematological malignancies between 2019 and 2023. The starting LMV dose was 480 mg daily, reduced to 240 mg daily for those receiving cyclosporin A co-administration. CMV DNA in the blood was measured by real-time polymerase chain reaction weekly for the first 2 months after transplantation, then every other week until the end of immunosuppressive treatment. LMV was continued to day +100 or to CMV reactivation.

Results: The median recipient age at the time of transplant was 51 (range: 20-71) years. All patients received grafts from peripheral blood, mostly for acute myeloid leukemia (60%). The median time from transplantation to LMV initiation was 3 (range: 0-24) days. While 55% of patients were transplanted from matched related donors, 32% had unrelated donors and 13% underwent haploidentical HSCT. Four patients (4%) had CMV "blips" while on LMV, but the drug was continued and repeated assays were negative. Only 2 patients (2%) experienced CMV reactivation while on LMV, on days 48 and 34 after HSCT, respectively. Seven patients (7%) developed late-onset CMV reactivation after a median of 124 days after HSCT (range: 118-152 days) and they were successfully treated with ganciclovir. CMV disease was not observed. Grade III-IV acute graft-versus-host disease occurred in 6 patients (6%) during LMV treatment. LMV treatment was free of side effects.

Öz

Amaç: Sitomegalovirüs (CMV) reaktivasyonu allojenik hematopoetik kök hücre transplantasyonu (HKHT) sonrasında hayatı tehdit eden bir komplikasyondur. Letermovir (LMV) kullanımının nakil sonrası sonuçları iyileştirdiği görülmektedir, ancak gecikmiş başlangıçlı CMV reaktivasyonu hala bir sorun olmaya devam etmektedir. Bu çalışmada, merkezimizde HKHT olan 93 CMV-seropozitif yetişkin hastada LMV profilaksisi ile ilgili ilk deneyimimizi bildiriyoruz.

Gereç ve Yöntemler: 2019-2023 yılları arasında hematolojik maligniteler için HKHT sonrası CMV profilaksisi olarak LMV başlanan 93 yetişkin CMV-seropozitif alıcının verilerini retrospektif olarak analiz ettik. Başlangıç LMV dozu günde 480 mg olup siklosporin A ile birlikte uygulananlar için günde 240 mg'a düşürülmüştür. Kandaki CMV DNA'sı gerçek zamanlı polimeraz zincir reaksiyonu ile transplantasyondan sonraki ilk 2 ay boyunca haftada bir, daha sonra immünosupresif tedavinin sonuna kadar iki haftada bir ölçülmüştür. LMV profilaksisi +100. güne kadar veya CMV reaktivasyonuna kadar devam ettirilmiştir.

Bulgular: Nakil sırasındaki ortanca alıcı yaşı 51 (aralık: 20-71) idi. Tüm hastalar, çoğunlukla miyeloid akut lösemi (%60) nedeniyle periferik kandan nakil yapılmıştır. Transplantasyondan LMV başlangıcına kadar geçen medyan süre 3 (aralık: 0-24) gündü. Hastaların %55'ine doku tipi uyumlu akraba vericilerden nakil yapılırken, %32'sine akraba olmayan vericiler ve %13'üne haploidentik HKHT uygulanmıştır. Dört hastada (%4) LMV kullanırken CMV "*blips*" görüldü, ancak ilaca devam edildi ve tekrarlanan testler negatif çıktı. Sadece 2 hastada (%2) LMV kullanırken, sırasıyla HKHT'den sonraki 34. ve 48. günlerde CMV reaktivasyonu görülmüştür. Yedi hastada (%7) HKHT'den ortanca 124 gün sonra (aralık: 118-152 gün) geç başlangıçlı CMV reaktivasyonu gelişmiş ve bu hastalar gansiklovir ile başarılı bir şekilde tedavi edilmiştir. Bu hastalarda CMV hastalığı gözlenmemiştir. LMV tedavisi sırasında 6 hastada (%6) grade III-IV akut graft-versus-host hastalığı meydana gelmiştir. LMV tedavisi boyunca yan etki görülmemiştir.

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Abstract

Conclusion: LMV prophylaxis was effective in preventing CMV reactivation with a favorable safety profile. CMV reactivation occurred mostly after LMV discontinuation; thus, extending the duration of prophylaxis beyond 100 days could be beneficial.

Keywords: Allogeneic hematopoietic stem cell transplantation, Antiviral prophylaxis, Cytomegalovirus reactivation, Letermovir

Öz

Sonuç: LMV profilaksisi, olumlu bir güvenlik profili ile CMV reaktivasyonunu önlemede etkili olmuştur. CMV reaktivasyonu çoğunlukla LMV kesildikten sonra meydana gelmiştir; bu nedenle profilaksi süresinin 100 günün ötesine uzatılması faydalı olabilir.

Anahtar Sözcükler: Allojenik hematopoietik kök hücre transplantasyonu, Antiviral profilaksi, Sitomegalovirüs reaktivasyonu, Letermovir

Introduction

Cytomegalovirus (CMV) reactivation remains a life-threatening complication after allogeneic hematopoietic stem cell transplantation (HSCT) [1,2]. It affects about 37% of patients and is associated with an increased risk of graft rejection, non-relapse mortality, and decreased overall survival [3,4,5,6]. Without an effective preventive strategy, CMV infection may occur in about 70% of recipients [7,8]. Definitions of CMV infection, reactivation, and disease are presented briefly in Table 1 [9,10,11,12].

Until today, the preferred preventive approach to CMV infection/disease was regular and careful monitoring of CMV blood viremia followed by prompt initiation of preemptive therapy (PET) upon detection of a significant rise in CMV viral load. Although this strategy results in a decline of CMV-related end-organ disease, the issue of frequent CMV reactivations in high-risk patients remains a challenge.

The treatment landscape changed in 2017 with the introduction of letermovir (LMV). The use of LMV as primary CMV prophylaxis has significantly improved clinical outcomes by decreasing the risk of clinically significant CMV (csCMV) infection in allotransplanted patients without causing significant side effects. Moreover, LMV has changed the pattern of CMV management policy in high-risk, CMV-seropositive patients from CMV surveillance and PET to a relatively safer and more effective preventive approach [13]. LMV was granted the recommendation of the European Conference on Infections in Leukemia and was approved in 2017 by the US Food and Drug Administration (FDA) and the European Medicines Agency for prevention of CMV infection/disease in CMV-seropositive HSCT recipients [11,14,15].

Although LMV as post-HSCT prophylaxis is now a well-established strategy, real-world data on delayed-onset CMV reactivations remain scarce. In this study, we report on our first experience with LMV prophylaxis in 93 CMV-seropositive adult patients receiving HSCT in our center.

Materials and Methods

The data of 93 adult patients (57 men) who received LMV prophylaxis between 2019 and 2023 were analyzed. Those who died or were lost to follow-up before the 100th day of observation were excluded from the analysis. Clinical data and transplantation details were obtained from our institutional database of medical records.

Table 1. Definitions of cytomegalovirus infection and disease.

Term	Definition
CMV infection	Isolation of CMV material (proteins or nucleic acid) in body fluid of any type or tissue sample
Primary CMV infection	CMV infection observed for the first time in an individual without known evidence of pre-transplant CMV exposure
Recurrent CMV infection	CMV infection in an individual with known previous evidence of CMV infection when the virus had not been detected during at least 4 consecutive weeks of monitoring, as a result of either reactivation of latent virus or virus reinfection (see below)
CMV reinfection	Detection of a different CMV strain than the one that caused the original CMV infection
CMV reactivation	Detection of two CMV strains (prior and current) that are found to be indistinguishable
Symptomatic CMV infection	Both presence of general symptoms and/or signs (e.g., fever, bone marrow suppression) and detection of CMV genetic material obtained using sensitive methods; no signs of CMV end-organ disease
CMV disease	Detection of CMV material by sensitive tests performed on tissue samples acquired through biopsy or other invasive methods, accompanied by the presence of symptoms and/or signs from the affected organ
"Blip"	An episode of isolated positive PCR assay results where preceding and following tests performed with 7-day intervals remain negative
Late-onset CMV reactivation	CMV reactivation after prophylaxis completion, i.e., beyond the 100th day after allotransplantation

CMV: Cytomegalovirus; PCR: polymerase chain reaction.

All analyzed patients were CMV immunoglobulin (Ig) G-seropositive and CMV IgM-negative before transplantation and received standard antiviral prophylaxis against the herpes simplex virus and varicella zoster virus with acyclovir, trimethoprim-sulfamethoxazole for *Pneumocystis jirovecii* prophylaxis, and fluconazole and/or posaconazole as fungal prophylaxis. The following factors were identified as signifying high risk for CMV reactivation: CMV seropositivity of the recipient (R) prior to transplantation regardless of donor (D) serostatus, cord blood as the stem cell source, unrelated or mismatched donor transplant, haploidentical transplant, use of T-cell depletion, use of corticosteroids at a dose of ≥1 mg/kg, and the occurrence/severity of acute or chronic graft-versus-host disease (GVHD) with treatment [13,16,17,18,19]. Irradiated, leukodepleted, and CMV-negative blood products were transfused after HSCT. GVHD prophylaxis consisted of a calcineurin inhibitor, i.e., either cyclosporin A or tacrolimus, with methotrexate and mycophenolate mofetil as needed. Post-transplant cyclophosphamide was provided in cases of haploidentical HSCT. Anti-thymocyte globulin was administered to every patient at high risk of GVHD (age >50 years, unrelated and/or female donor). The Child-Pugh score was used to rule out severe hepatic impairment. All patients were also screened for the presence of severe kidney failure or any other exclusion criteria. The dose of LMV was adjusted for cyclosporin A co-administration. LMV was continued until day +100 after transplantation or to CMV reactivation.

From the time of neutrophil engraftment, defined as absolute neutrophil count of $\geq 0.5 \times 10^9$/L for 3 consecutive days, patients were screened for CMV reactivation. CMV DNA in the blood was measured using real-time polymerase chain reaction (PCR) weekly for the first 2 months after transplantation, then every other week until the end of immunosuppressive treatment. LMV was continued to day +100 after HSCT or to CMV reactivation. The lower limit of CMV detection was 1 copy/µL.

The detection of measurable CMV DNAemia increasing in 2 consecutive assays was treated as CMV reactivation and PET with (val)ganciclovir [(V)GCV] was then initiated. "Blips" were defined as episodes of isolated positive CMV PCR test results where both the preceding and the succeeding tests performed with 7-day intervals remained negative. When a blip was confirmed, LMV was continued. Late-onset CMV reactivation was defined as virus reactivation after LMV completion. Acute GVHD (aGVHD) was diagnosed and graded according to standard criteria [20,21].

Results

Median recipient age at transplant was 51 (range: 20-71) years. All analyzed patients were CMV IgG-seropositive before transplantation. Thirty-five patients (38%) received an allograft from a seronegative donor (D-/R+) while the remaining patients had seropositive donors (D+/R+). In 76% (n=71) of the cases, myeloid neoplasm was the primary underlying disease, and most patients were transplanted for myeloid acute leukemia (n=60). Peripheral blood was the stem cell source for all transplanted patients. Fifty-one patients (55%) received grafts from human leukocyte antigen (HLA)-matched siblings, 30 patients (32%) were transplanted from unrelated 10/10 HLA-matched (n=16) or 8-9/10 HLA-mismatched (n=14) donors, and 12 patients (13%) underwent haploidentical transplantation. About half of the patients (n=47) received reduced-intensity conditioning, whereas myeloablative conditioning was administered to other patients. The patients' characteristics are summarized in Table 2.

The median time from transplantation to LMV initiation was 3 (range: 0-24) days and the drug was administered orally for all patients. Fifty-two (56%) patients received LMV at 240 mg daily due to concomitant use of cyclosporin A while LMV at 480 mg a day was administered to the remaining 41 patients. One patient's treatment was temporarily interrupted due to severe post-transplant mucositis with dysphagia.

Table 2. Patients' characteristics.

Variable	n=93
Median age, years [range]	51 [20-71]
Male sex, n (%)	57 (61)
Diagnosis, n (%)	
• **Myeloid neoplasms**	71 (76)
AML	56 (60)
MDS	7 (8)
CML	3 (3)
MF	3 (3)
CMML	2 (2)
• **Lymphoid neoplasms**	18 (19)
ALL	11 (12)
DLBCL	2 (2)
BPDCN	2 (2)
MM	1 (1)
BL	1 (1)
ALCL	1 (1)
• **Others**	4 (4)
SAA	4 (4)
Donor, n (%)	
• Sibling	51 (55)
• Unrelated	30 (32)
• Haploidentical	12 (13)
Conditioning, n (%)	
• Myeloablative	46 (49)
• Reduced intensity	47 (51)
CMV serostatus, n (%)	
• D+/R+	58 (62)
• D-/R+	35 (38)

AML: Acute myeloid leukemia; MDS: myelodysplastic syndrome; CML: chronic myeloid leukemia; MF: myelofibrosis; CMML: chronic myelomonocytic leukemia; ALL: acute lymphoblastic leukemia; DLBCL: diffuse large B-cell lymphoma; BPDCN: blastic plasmacytoid dendritic cell neoplasm; MM: multiple myeloma; BL: Burkitt lymphoma; ALCL: anaplastic large cell lymphoma; SAA: severe aplastic anemia; CMV: cytomegalovirus; D: donor; R: recipient.

Four patients (4%) were found to have CMV "blips" at a median of 56 (range: 30-90) days after HSCT with a median number of 31 (range: 16-46) copies/µL, but repeated PCR assays were found to be negative and LMV was continued. Only 2 patients (2.2%) had reactivated CMV during LMV. The first patient had reactivated CMV on day +34 with CMV PCR of 188 copies/µL. The second patient (the one for whom LMV was interrupted for 10 days) had reactivated CMV on day +48 with 232 copies/µL. Both patients had the LMV discontinued and received treatment with GCV with CMV eradication. Seven patients (7%) developed late-onset CMV reactivation at a median of 124 (range: 118-152) days after HSCT with a median CMV load of 81 (range: 11-453) copies/µL. CMV reactivations were treated successfully with (V)GCV.

Six patients (6%) developed grade III-IV aGVHD while on LMV. Despite triple immunosuppressive treatments including a JAK2-inhibitor, ruxolitinib, none of them developed CMV reactivation. LMV was well tolerated and only mild side effects were observed. Nausea, decreased appetite, fatigue, and abdominal pain were among the commonest, but other medications including antibiotics, antifungals, and immunosuppressive agents were being simultaneously administered. No severe or life-threatening adverse events or signs of myelotoxicity or nephrotoxicity were reported.

Three patients qualified for secondary HSCT due to secondary graft failure. Six patients died within the first year after HSCT: 5 due to early relapse and 1 from severe pneumonia. Two of them had previously experienced CMV reactivation. The other patients remain in long-term follow-up and are in good condition overall.

Discussion

The efficacy of primary prophylaxis with LMV in preventing CMV infection in HSCT settings was first demonstrated in a phase II trial [22]. Soon afterwards, Marty et al. [23] performed a pivotal phase III trial including 565 CMV-seropositive allo-recipients. This trial showed that csCMV infection occurred almost 2 times less frequently in the LMV group (37.5% of cases) compared to the placebo group (60.6%) at 24 weeks after HSCT. It also showed that prophylaxis with LMV improved post-transplant survival without causing significant side effects [23]. The success of that phase III trial led to LTV's approval by the FDA and to a shift in anti-CMV policy towards prophylaxis. Post hoc analysis demonstrated that in the LMV group all-cause mortality was lower than in the placebo group not only at week 24 but also at week 48 after HSCT. It has been suggested that the reduction in all-cause mortality achieved by LMV might be related to the delay in the onset of csCMV infection/disease until immune reconstitution is advanced enough to respond to the viral invasion [24,25].

Real-life experiences with the efficacy and safety of LMV as primary CMV prophylaxis reported by transplant centers worldwide were in line with the results of the pivotal study by Marty et al. [20,26,27,28,29,30,31]. According to recent meta-analyses and literature reviews, primary prophylaxis with LMV for adult HSCT recipients reduced the incidence of CMV reactivation, infection, and disease at both day +100 and day +200 compared to controls [24,32,33]. Moreover, no delay in hematological reconstitution and no signs of myelotoxicity or nephrotoxicity were observed in published reports presenting beneficial safety profiles. Our analysis is consistent with those real-life data.

In the aforementioned phase III trial, patients with a high risk of CMV reactivation benefited more from LMV prophylaxis than patients with lower risk. D/R CMV serological status remains the main risk factor influencing the incidence and mortality of CMV reactivation/disease after HSCT [1,16,34,35]. It has been demonstrated that seropositive recipients are more likely to experience CMV reactivation if they received a graft from a seronegative donor than from a seropositive one [36,37,38]. Nevertheless, CMV reactivation occurs in up to 70% of CMV IgG seropositive allo-recipients regardless of donor status according to some recent studies, and LMV prophylaxis is therefore recommended for all CMV seropositive recipients [1,11,39]. In our study, 5 patients out of 7 who had reactivated CMV after 100 days had received grafts from CMV-seronegative donors. This is consistent not only with the results from the pivotal trial by Marty et al. [23] but also with observations from the meta-analysis by Vyas et al. [24], where LMV use was found to be particularly beneficial for high-risk patients [30,40]. Real-world data have shown not only a significant reduction in the risk of any CMV-related complications in all analyzed reports but also a decreased demand for the use of PET, shortened hospitalizations, fewer re-admissions to the hospital, and fewer concurrent complications, particularly fungal or bacterial infections. This, in turn, is associated with a potential economic benefit [41,42].

GVHD increases the risk of CMV reactivation and vice versa. Moreover, GVHD contributes to significant morbidity and mortality, especially when it requires prolonged immunosuppressive treatment that impairs the immune defense of the host [1,11]. It has been suggested that LMV prophylaxis also improves transplantation outcomes in patients with aGVHD. According to recent research, patients with aGVHD had significantly fewer csCMV infections while receiving LMV prophylaxis compared to patients who did not receive LMV [40]. Moreover, improved GVHD-free, relapse-free survival was also demonstrated [43].

Despite the high efficacy of LMV in preventing csCMV infection/disease after HSCT, a higher frequency of delayed-onset CMV

infections has been observed after LMV discontinuation, highlighting the potential role of extended LMV prophylaxis [29,44,45,46,47]. The significance of prolonged LMV prophylaxis for high-risk patients was already addressed by Marty et al. [13]. Discontinuation of LMV on day 100 after HSCT has also been shown to increase CMV-related mortality between days 180 and 364 [46]. A recently published study by Dadwal et al. [48] showed that extending LMV prophylaxis to 200 days after HSCT significantly reduced the incidence of csCMV infections compared to a placebo (2.8% vs. 18.9%) in the high-risk patient group. Despite prolonged administration, LMV was well tolerated and demonstrated a good safety profile with adverse effects similar to those of the placebo. The findings from this trial also suggest that a longer duration of LMV prophylaxis might be particularly beneficial for patients with delayed CMV T-cell reconstitution [41]. In our study, we observed that LMV was effective at reducing csCMV infection/disease during the first 100 days after HSCT, but the incidence of CMV reactivation increased thereafter.

Study Limitations

A potential limitation of this study is its single-center design and short follow-up period. However, the strength of our analysis lies in the fact that we provided real-world data regarding a relatively large population with high CMV seroprevalence compared to other single-arm retrospective cohort studies. More data are needed to confirm our findings in Polish patients.

Conclusion

LMV prophylaxis was effective in preventing CMV reactivation with a favorable safety profile. CMV reactivation occurred most often after LMV discontinuation; thus, extending the duration of prophylaxis beyond 100 days could be beneficial.

Ethics

Ethics Committee Approval: The work described in this article was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans, EU Directive 2010/63/EU for animal experiments, and the uniform requirements for manuscripts submitted to biomedical journals.

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Authorship Contributions

Surgical and Medical Practices: A.W.K., K.B., A.K., I.N., P.Z.; Concept: M.W., G.H.; Design: M.W.; Data Collection or Processing: M.W., A.W.K., K.B., A.K., I.N., P.Z.; Analysis or Interpretation: M.W., G.H.; Literature Search: M.W.; Writing: M.W., G.H.

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