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ORIGINAL RESEARCH ARTICLE

Real-life experiences of letermovir prophylaxis for cytomegalovirus infection in patients after hematopoietic stem cell transplantation: Polish Acute Leukemia Group (PALG) analysis

Anna Łojko[1*], Jan Styczyński[2], Barbara Nasiłowska-Adamska[3], Joanna Mańko[3], Krzysztof Kałwak[4], Patrycja Mensah-Glanowska[5], Jarosław Dybko[6], Maciej Majcherek[7], Anna Czyż[7], Agnieszka Pluta[8], Lidia Gil[1]

[1]Department of Hematology and Bone Marrow Transplantation, Poznan University of Medical Sciences, Poznań, Poland
[2]Department of Pediatric Hematology and Oncology, *Collegium Medicum,* Nicolaus Copernicus University in Toruń, Jurasz University Hospital 1, Bydgoszcz, Poland
[3]Department of Hematology, Institute of Hematology and Transfusion Medicine in Warsaw, Warszawa, Poland
[4]Department of Pediatric Bone Marrow Transplantation, Oncology and Hematology, Wroclaw Medical University, Wrocław, Poland
[5]Department of Hematology, *Collegium Medicum,* Jagiellonian University, Kraków, Poland
[6]Department of Hematology and Transplantology, Lower Silesian Oncology Center, Wrocław, Poland
[7]Department of Hematology, Blood Neoplasm and Bone Marrow Transplantation, Wroclaw Medical University, Wrocław, Poland
[8]Department of Hematology, Medical University in Lodz, Łódź, Poland

Abstract

Introduction: Letermovir (LMV) is a new, cytomegalovirus (CMV)-specific, antiviral drug, approved in 2018 for CMV prophylaxis in patients after allogeneic hematopoietic transplantation. The introduction of letermovir prophylaxis has changed the management of CMV infection: it has reduced the incidence of CMV infections and CMV-related complications, and also improved the overall survival in CMV seropositive patients. However, until recently, due to its high treatment cost, prophylaxis with letermovir has not beeen a standard of care in Poland.

Material and methods: To confirm the effectiveness and safety of letermovir prophylaxis, we collected real-life data from eight Polish transplant centers, in which a total of 53 patients were treated with letermovir, including off-label use.

Results: LMV is characterized by low toxicity and good tolerability. There were no reports of special adverse events caused by LMV.

Conclusions: Our experiences confirm the effectiveness and safety of letermovir prophylaxis, and suggest that this prophylaxis should be started as soon as possible after the infusion of stem cells, preferably no later than day 14. Moreover, our findings indicate that some patients could benefit from extended letermovir prophylaxis beyond 100 days after transplant.

Key words: cytomegalovirus infection, allogeneic hematopoietic stem cell transplantation, letermovir, antiviral prophylaxis

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*Address for correspondence: Anna Łojko, Department of Hematology and Bone Marrow Transplantation, Poznan University of Medical Sciences, Szamarzewskiego 84, 60–569 Poznań, Poland, e-mail: lojko.ania@gmail.com

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Introduction

Cytomegalovirus (CMV) infection remains a clinically important complication after allogeneic hematopoietic stem cell transplantation (allo-HSCT), which can adversely affect transplant outcome [1]. CMV seropositivity in HSCT recipients, as well as early CMV reactivation after HSCT, can significantly increase the risk of non-relapse mortality [2, 3].

Until recently, the management of CMV infection in post-HSCT patients was based on the monitoring of CMV DNA-emia in blood by real-time quantitative polymerase chain reaction (RT-qPCR) and by using pre-emptive therapy [pre-emptive therapy (PET)] to prevent CMV disease. The use of gancyclovir or valgancyclovir as a CMV prophylaxis was limited by significant myelosuppression, and has never become a standard of care in hematopoietic cell transplantation [1].

The introduction of letermovir (LMV) has changed the management of CMV infection. LMV is licensed and recommended for prophylaxis of CMV infection in allogeneic hematopoietic cell transplant seropositive adults, up to 100 days after HSCT, showing a reduction of CMV as a clinically significant infection [4]. Clinically significant CMV infection is defined as a viremia which requires antiviral pre-emptive therapy (PET) or as a CMV disease [4]. LMV has a unique mechanism of action, different from other antiviral drugs, which makes it a safe agent for transplant recipients [5]. In Poland, LMV has not been used routinely in CMV seropositive patients after allogeneic HSCT due to its high cost, but we hope this will change soon.

Material and methods

As part of Polish Adult Leukemia Group (PALG) cooperation among Centers, we collected data on LMV use in patients treated with allogeneic HSCT in eight Polish Transplant Centers between 2019 and 2021. We collected all LMV cases, including those where LMV was used off-label. We analyzed the efficacy and safety of treatment. The clinical data and transplantation details were obtained from institutional medical records. Prophylaxis failure was defined as a requirement of antiviral PET or as the development of CMV disease. CMV-DNA-emia in blood was monitored using RT-qPCR at least weekly. PET was initiated according to transplant center practice.

Results

Data from 53 patients was reported, including 46 adults and seven children, and comprising 32 females (62.7%) and 20 males (37.7%). The median age of patients was 38 (range 5–70) years. Patients were transplanted mainly for acute leukemia (n = 32) (Table I). All patients were CMV seropositive, and the majority of donors (60.4%) were CMV seronegative.

Table I. Patient characteristics

Parameter	Number of patients — 53 (100%)
Median age (range) — 38 (5–70):	
• <18 years	7 (13.2)
• ≥18 years	46 (86.8)
Gender:	
• male	20 (37.7)
• female	33 (62.3)
Diagnosis:	
• acute myeloid leukemia	20 (37.7)
• acute lymphoblastic leukemia	12 (22.6)
• myeloproliferative neoplasm	4 (7.5)
• myelodysplastic/ /myeloproliferative	2 (3.8)
• myelodysplastic syndrome	2 (3.8)
• SAA and PNH	2 (3.8)
• non-Hodgkin lymphoma	5 (9.4)
• Hodgkin lymphoma	2 (3.8)
• other	4 (7.5)
Donor:	
• sibling	8 (15.1)
• unrelated	31 (58.5)
• haploidentical	14 (26.4)
Conditioning:	
• myeloablative	29 (54.7)
• reduced intensity	24 (45.3)
ATG	33 (62.3)
CMV status:	
• patient +/donor +	21 (39.6)
• patient +/donor –	32 (60.4)
Second HSCT	8 (15.1)

SAA — severe aplastic anemia; PNH — paroxysmal nocturnal hemoglobinuria; ATG — antithymocyte globulin; CMV — cytomegalovirus; HSCT — hematopoietic stem cell transplantation

LMV dose and administration

LMV was administered orally in all patients. Most adults (n = 43) received a reduced dose of LMV, 240 mg per day, due to concomitant use of cyclosporin (CSA) as a graft-versus-host disease prophylaxis. Only three adult patients received a full dose of LMV 480 mg per day and tacrolimus instead of CSA. Among children, four received a dose of 240 mg per day, two patients received 120 mg per day, and one patient 60 mg per day. All children received CSA as a graft-versus-host disease prophylaxis.

Primary or secondary prophylaxis

A great majority of the patients (86.8%) received LMV as a primary prophylaxis of CMV infection after HSCT according to registration indication. Three of them had been previously diagnosed and treated for CMV infection prior to this transplantation, so they were included in the primary prophylaxis group. In this group of patients, LMV was started between the first day after HSCT up to day 31, with a median between HSCT and treatment initiation of six days. In 19 patients, LMV prophylaxis was started on the first day after HSCT.

In seven cases (13.2%), LMV was used as a secondary prophylaxis after previous CMV reactivation after this transplantation. In most of these patients (85.7%), CMV reactivation occurred up to 30 days after HSCT. In this group of patients, LMV was started between days 47 and 144 after HSCT (median day 66). In all patients, this was after the completion of CMV infection treatment. Three patients experienced more than one reactivation, two of them with graft failure symptoms, and required longer CMV treatment. All these patients were treated with gancyclovir, and three of them also required a second or a third line of CMV treatment, which comprised foscarnet and/or cidofovir.

Duration of treatment

The median duration of LMV treatment was 90 days, range 6 days to over 270 days. In seven cases, LMV was stopped prematurely and unplanned. The reasons for this discontinuation were as follows: relapse of the disease in one patient after 20 days, severe infection complication in three patients after 6, 8 and 16 days, and reactivation of CMV infection in four patients. CMV infection was recognized on days 6, 62, 71 and 75 of LMV administration. Two patients restarted LMV as a secondary prophylaxis after PET completion. In one patient, LMV was changed to gancyclovir prophylaxis after 27 days.

In patients who completed their planned LMV therapy, the median duration of treatment was 97 days, range 27 to over 270 days. Most patients received LMV for 84 or 112 days due to the number of tablets in a pack (28 tablets per pack). Five patients received LMV for more than 112 days.

CMV reactivation and pre-emptive treatment

Clinically significant CMV infection requiring pre-emptive treatment occurred in four patients receiving primary prophylaxis (8.7%), and in no one receiving secondary prophylaxis. CMV infection was recognized on days 6, 62, 71 and 75 of LMV administration. In one patient (1.9%), CMV disease was diagnosed. Gancyclovir or valgancyclovir were used as first line treatment, and in one patient foscarnet was used as a second-line. Two patients restarted LMV after clearance of CMV.

In four patients, CMV infection was recognized after completion of LMV prophylaxis, and time to reactivation ranged from one to three months after completion of LMV.

Table II. Cytomegalovirus (CMV) infection during and after completion of prophylaxis

CMV infection	Primary prophylaxis	Secondary prophylaxis
Number of patients	46	7
During prophylaxis:		
• CMV-DNAemia/single blip	1	1
• PET	3	0
• CMV disease	1	0
After completion of prophylaxis:		
• CMV-DNAemia/single blip	3	0
• PET	4	2
• CMV disease	0	0

PET — pre-emptive therapy

In three cases, a single blip of CMV-DNA was found which did not require treatment.

There was no CMV infection in patients during secondary prophylaxis. Two patients were diagnosed with CMV infection after the completion of secondary prophylaxis — one and six months after completion (Table II).

Safety of LMV prophylaxis

There were no reports of special adverse events caused by LMV. In patients who started LMV early, before reconstitution of hematopoiesis, the median time to granulocyte and platelet reconstitution was 17 days. Two patients died without reconstitution of hematopoiesis. In total, 10 out of 53 patients (18.8%) died: five due to infection, four due to relapse of disease, and one due to graft-versus-host disease (GvHD). Among patients who died due to infection, two were without reconstitution in cytopenia (bacterial infection), one was on day 54 after HSCT (pneumonia, possibly fungal), and two were more than 100 days after HSCT (one bacterial, one fungal infection). No one died due to CMV disease. No one patient stopped LMV due to adverse reactions. Median follow-up was 8 months, range 1–24.

Discussion

CMV infection is a common complication in immunocompromised patients, especially after alloHSCT, in both adults and children [6]. In healthy individuals, a primary infection of CMV is usually asymptomatic or mildly symptomatic. In patients after HSCT, primary CMV infection or CMV reactivation can lead to serious complications and is associated with increased morbidity and mortality. The most frequent clinical manifestations are pneumonia, enteritis, hepatitis, bone marrow suppression, and retinitis [7]. CMV seropositivity before transplantation in both recipient and donor is associated with decreased overall survival, which is most likely mediated through both direct and indirect effects of the virus [8]. Also, CMV viremia is associated with an

increased risk of overall and non-relapse mortality in the first year after HSCT, independently of the use of PET [9].

Despite great advances in treating CMV infection in patients after allo-HSCT, it remains a challenge, especially as most drugs are highly toxic and can cause myelosuppression, kidney or liver damage, or other adverse events.

LMV is the first antiviral drug with a completely different mechanism of action compared to gancyclovir, foscavir and cidofovir. LMV inhibits the terminal phase of the virus life cycle by targeting the subunit of the terminase enzyme complex. Its antiviral activity is highly specific to CMV, and no cross-resistance has been reported as far. Due to this specific mechanism of action, LMV is characterized by low toxicity and good tolerability, although attention should be paid to the interactions between LMV and other drugs (e.g. calcineurin inhibitors, azoles, or JAK2 inhibitors) [10].

LMV is licensed and recommended for prophylaxis of CMV infection in allogeneic hematopoietic cell transplant adults, up to 100 days after HSCT, but there is also data regarding off-label use of LMV such as: secondary prophylaxis, pre-emptive therapy, therapy of CMV disease, primary prophylaxis in seronegative recipients, use in children, and use for longer periods and repeated courses of use. None of these has resulted in increased toxicity [11].

The safety and efficacy of LMV have not been established in pediatric patients below 18 years of age, but many published cases have described the use of LMV in children, both for prophylaxis and for treatment of CMV infections, including those resistant to other drugs [12–14]. There is no data on pharmacokinetics in children, but the dose can be proportionally adjusted for children's body weight based on adult pharmacokinetic data. In most cases, children weighing more than 50 kg receive the adult dose.

The effectiveness of LMV in preventing CMV infection has been proven in a pivotal phase III clinical trial where LMV significantly reduced the incidence of clinically significant CMV infection through week 24 after allo-HCT when compared to a placebo (18.9% vs. 44.3%, p <0.001) [4]. Furthermore, patients receiving LMV had a lower risk of all-cause mortality at 24 weeks after HSCT compared to a placebo [15]. These results have been confirmed in a real-world study and it has also been shown that LMV can shorten the duration of anti-CMV PET [16–18].

The use of LMV prophylaxis is also cost-effective by reducing the cost of PET as well as the costs of hospital readmission, antibiotics, antifungal drugs, and supportive therapy [19].

Despite progress in monitoring and treating CMV infection, there is still no consensus as to the cut-off value of viral DNA load for the initiation of antiviral therapy [1]. Frequently the cut-off value is above 1,000–1,500 IU/mL, or CMV DNA load doubling time ≤2 days, whichever of these occurred first. But some authors advocate starting PET at lower CMV DNA loads to reduce time of CMV DNAemia, while others suggest delaying the initiation of PET until higher levels of blood CMV DNA are reached in order to minimise drug-related toxicity risk [20]. Moreover, some CMV DNAemia episodes resolve spontaneously. These self-resolving episodes of CMV DNAemia are called 'blips' [20]. Blips are defined as the presence of CMV DNA at any level in a single plasma specimen, preceded and succeeded by a negative PCR, usually drawn seven days apart, and not requiring PET. In the LMV era, careful monitoring of blips is especially important so as not to terminate prophylaxis prematurely, as blips may be non-replicating CMV DNA resulting from the specific mechanism of LMV action [21].

LMV is characterized by excellent tolerance and the frequency of most adverse events is comparable to a placebo group. In our study, due to its retrospective nature, some typical adverse events such as nausea or vomiting probably were not classified as being related to LMV. No myelotoxicity was reported, which is particularly important in the context of the toxicity of other anti-CMV drugs.

Conclusions

Our analysis confirms the safety and efficacy of LMV in the prophylaxis of CMV infection in patients after HSCT, and also the off-label use of LMV such as: secondary prophylaxis, use in children, and using longer than 100 days.

Based on the results of our study, we draw two conclusions.

Firstly, we conclude that LMV prophylaxis should be started as soon as possible after the infusion of stem cells, preferably before engraftment, i.e. before day 14 after transplant, as we have observed that in some patients early CMV reactivation preceded the initiation of prophylaxis. This is especially important since the results of many studies do not indicate that LMV has any influence on reconstitution time.

Our second conclusion concerns the duration of LMV prophylaxis. Presumably, some patients may benefit from prophylaxis longer than 100 days because extended LMV treatment could also prevent late CMV reactivation. In our group, as many as six patients experienced CMV infection after the completion of prophylaxis. Also, in a pivotal phase III study, the incidence of clinically significant CMV infection increased in the letermovir group shortly after the discontinuation of therapy [4, 22]. In an ongoing study, extended LMV prophylaxis from 100 to 200 days is being evaluated, and the results will be known soon.

Authors' contributions

AŁ, JS and LG conceived the idea for the study. All authors were involved in data collection. AŁ analyzed the data and wrote the manuscript. All authors revised and approved the final version.

Conflict of interest
None.

Financial support
None.

Ethics
The work described in this article has been 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; Uniform Requirements for manuscripts submitted to Biomedical journals.

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