

Letermovir for Cytomegalovirus Prevention in Patients Undergoing Hematopoietic Cell Transplantation

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Abstract

Cytomegalovirus (CMV) is a double-stranded DNA virus that infects (seropositive on screening) more than half of adults by age 40. However, reactivation of detectable viral load (CMV reactivation) typically occurs only in immunocompromised patients. Notably, CMV reactivation after allogeneic hematopoietic cell transplant (HCT) can increase treatment-related mortality almost 2-fold compared to patients who do not have reactivation. Historically, prevention of CMV reactivation mainly included the preemptive strategy of serial monitoring of viral load and initiating an antiviral once the viral load became elevated in an effort to prevent end-organ disease. The major limitations of the antiviral agents utilized in preemptive therapy are myelosuppression and renal toxicity. In 2017, a first-in-class viral terminase complex subunit inhibitor, letermovir, became the only U.S. Food & Drug Administration–approved medication to prevent CMV reactivation after allogeneic HCT (e.g., as prophylaxis). In a phase III trial, patients who were randomized to letermovir prophylactically had decreased rates of CMV viremia leading to preemptive therapy. The purpose of this article is to describe the need for safe and effective medication to prevent CMV reactivation, the clinical efficacy of letermovir, and the impact oncology advanced practitioners can play in reducing CMV reactivation in patients undergoing allogeneic HCT.

Cytomegalovirus (CMV) is a ubiquitous double-stranded DNA herpes virus that infects over 50% of adults by age 40 (Bhat, Joshi, Sarode, & Chavan, 2015). Transmission most commonly occurs through direct contact with bodily fluids (e.g., saliva or urine), sexual contact, perinatally (in utero, through the birth canal or through breast milk), or blood and tissue products (Centers for Disease Control and Prevention, 2018). Most infected immunocompetent individuals will be asymptomatic and the virus will persist in a latent stage. While CMV can

infect any cell, the latent virus is most commonly found in the arterial vasculature (Bhat et al., 2015).

Patients who are immunocompromised, such as allogeneic hematopoietic cell transplant [HCT] patients, have the potential for reactivation of latent CMV. Cytomegalovirus reactivation usually occurs within the first 100 days after transplant and can manifest as viremia (detection of CMV DNA by polymerase chain reaction) or CMV disease (end-organ disease caused by CMV). Cytomegalovirus disease in HCT most commonly affects the gastrointestinal tract and lungs. True incidence of CMV infection (viremia and/or disease) after HCT is unknown but has been estimated to be as high as 70%. Risk factors for CMV reactivation and infection include serologic status of the donor/recipient (donor negative/recipient positive and donor positive/recipient positive), human leukocyte antigen (HLA) mismatch (HLA-A, -B, and -DR mismatch), older age, use of antithymocyte globulin, recipient of total body irradiation, and transplantation with umbilical cord blood (Bhat et al., 2015; Boeckh & Ljungman, 2009). For patients who are seropositive, transplant-related mortality can be as high as 50% and CMV reactivation can increase treatment-related mortality by almost 2-fold compared to patients who do not have CMV reactivation (Broers et al., 2000; Teira et al., 2016).

Historically, prevention of CMV included serial monitoring of viral load and initiating ganciclovir (Cytovene), or alternative agents such as foscarnet (Foscavir) or cidofovir (Vistide), upon elevation of the viral load, which was termed “preemptive therapy.” Monitoring viral load is important in order to initiate antiviral therapy early to prevent the development of higher levels of viremia and potential end-organ damage.

A major limitation of this strategy is a lack of an established viral load threshold by which to initiate preemptive therapy. Another limitation is the adverse effects of these medications. Ganciclovir has a black box warning for myelosuppression, which is not ideal in a patient for whom stem cell engraftment is desired. Foscarnet has a black box warning for renal impairment, which can cause substantial electrolyte abnormalities and limits its use. Cidofovir carries black box

warnings for both neutropenia and nephrotoxicity (Bhat et al., 2015).

While some antivirals have been studied for prophylaxis of CMV replication (e.g., acyclovir [Sitavig] and valacyclovir [Valtrex]), studies failed to show significant benefit in preventing CMV disease, reactivation, and all-cause mortality. Despite promising phase II studies comparing maribavir and brincidofovir to placebo as prophylactic medications, subsequent phase III studies failed to show significant benefit in preventing CMV disease, reactivation, or preemptive therapy (Chen, Cheng, Hammond, Einsele, & Marty, 2018; Gaglemann, Ljungman, Styczynski, & Kröger, 2018). Similarly, studies involving prophylactic administration of intravenous immune globulin also failed to show a significant benefit (Winston et al., 1987; Zikos et al., 1998).

Due to the lack of effective prophylaxis strategies, as well as concerns with toxicities of preemptive therapies and lack of standardized thresholds for which to initiate such therapy, a need exists for a safe and effective medication to prevent CMV reactivation. Letermovir (Prevymis) recently became the only U.S. Food & Drug Administration (FDA)-approved medication for CMV prophylaxis in seropositive patients undergoing HCT.

MECHANISM OF ACTION AND PHARMACOKINETICS

Letermovir is a first-in-class viral terminase complex subunit pUL51, pUL56, and pUL89 inhibitor. Normally, these subunits are involved in viral replication/packaging and have ATPase activity. It has been proposed these subunits facilitate viral cleavage after genome replication and provide energy for viral DNA spooling into capsids (Borst et al., 2005). Therefore, by inhibiting this mechanism, letermovir makes CMV incapable of spreading to and infecting other cells. Ganciclovir inhibits subunit pUL97, while foscarnet and cidofovir inhibit subunit pUL54. These subunits work by inhibiting DNA polymerase to prevent viral replication (El Chaer, Shah, & Chemaly, 2016). Since letermovir has a novel mechanism, if resistance were to arise, it would not confer cross resistance to ganciclovir, foscarnet, or cidofovir. Notably, letermovir is highly specific only for CMV with no activity against other herpesvirus, including her-

pes simplex virus (HSV; Melendez & Razonable, 2015). Therefore, patients receiving letermovir also require separate medication (e.g., acyclovir) as prophylaxis for HSV.

In HCT patients receiving 480 mg orally once daily, the bioavailability was approximately 35%, which was not affected by food. When cyclosporine was coadministered with 240 mg once daily, the bioavailability increased to approximately 85%. The estimated volume of distribution is 45.5 L, and it is extensively bound to human plasma proteins. Letermovir does not undergo phase 1 metabolism by cytochrome P450 enzymes and partly undergoes glucuronidation by UGT1A1/1A3. The terminal half-life is 12 hours and is excreted by the feces as the unchanged parent compound (Merck & Co., Inc., 2017).

CLINICAL EFFICACY

Letermovir approval was based on a phase III, international, randomized, double-blind trial. Patients had undergone an allogeneic HCT, were CMV-seropositive, and had not received antiviral agents with CMV activity. Patients were randomized 2:1 to receive letermovir at 480 mg once daily ($n = 373$; 240 mg if they were on concomitant cyclosporine) or placebo ($n = 192$). Sixty-one percent of the patients in the letermovir group and 59% in the placebo group had a seropositive donor. High-risk patients for CMV reactivation and disease were defined as meeting at least one of the following criteria: related donor with at least one mismatch at HLA-A, -B, or -DR; unrelated donor with at least one mismatch at HLA-A, -B, -C, or -DRB1; haploidentical donor; umbilical cord blood stem-cell source; ex vivo T-cell depleted graft; or graft-vs.-host disease grade ≥ 2 leading to use of prednisone at ≥ 1 mg/kg/day (or equivalent). All other patients were classified as low risk. Similar numbers of high-risk patients were present in the letermovir and placebo groups, 32.4% and 28.1%, respectively.

Patients started prophylaxis with the study medication a median of 9 days post transplant (range, 0–29 days) and continued through week 14 post transplant. Patients received letermovir for a median of 82 days (range, 1–113 days) and placebo a median of 56 days (range, 4–115 days). The most common reasons for drug discontinuation were

death and withdrawal of consent (37 patients [10%] and 23 patients [6%] for letermovir and 28 patients [14%] and 16 patients [8%] for placebo, respectively). Forty-eight patients (13%) and 22 patients (11%) in the letermovir and placebo groups, respectively, had detectable CMV at randomization. Three hundred and twenty-five patients who received letermovir and 170 patients who received placebo were included in the efficacy population.

The primary endpoint was clinically significant CMV infection, which was defined as CMV viremia leading to preemptive therapy or CMV disease through week 24 post transplant. If a patient discontinued the treatment for any reason, they were imputed as having a primary endpoint event. Primary endpoint (CMV infection developed or imputed as having the primary endpoint) occurred in 37.5% in the letermovir group compared to 60.6% in the placebo group ($p < .001$). Similar numbers of patients in the two efficacy groups discontinued the trial or had missing data (20% in the letermovir group and 18.8% in the placebo group), while documented clinically significant CMV infection occurred in 17.5% vs. 41.8% of patients. Cytomegalovirus disease was not significantly different between the groups, occurring in only 1.5% and 1.8% of patients in the letermovir and placebo groups, respectively. The subgroup analysis showed letermovir prophylaxis provided a significant reduction in clinically significant CMV infections for patients stratified as high risk or low risk (Marty et al., 2017).

A recent post-hoc analysis of phase III data investigated the effects of letermovir on all-cause mortality in CMV seropositive patients who had undergone an allogeneic HCT. All-cause mortality was defined as death due to any reason and evaluated 24 and 48 weeks post allogeneic HCT. At 24 weeks post allogeneic HCT, all-cause mortality was significantly lower in the letermovir group compared to the placebo group (12.1% vs. 17.2%, respectively), but was not significantly lower at 48 weeks (23.8% vs. 27.6%, respectively). In patients who received placebo, 48-week all-cause mortality was higher in patients who developed CMV infection compared to patients who did not develop CMV infection (31% vs. 18.2%, respectively). In patients who received letermovir, 48-week all-cause mortality was similar in patients who did and did

not develop CMV infection (15.8% vs. 19.4%, respectively). The most common reasons for death 48 weeks post HCT in the letermovir and placebo groups were acute myeloid leukemia (3.7% and 5.9%), graft-vs.-host disease (2.2% and 4.1%), and sepsis (1.8% and 2.4%; Ljungman et al., 2019).

DOSING, ADMINISTRATION, AND MODIFICATIONS

The recommended dose of letermovir is 480 mg orally once daily without regard to meals. Prophylaxis with letermovir may be initiated any day between the day of transplant up until 28 days after transplant and is recommended to continue through day 100 post transplant. If cyclosporine will be given concomitantly, letermovir should be given as 240 mg orally once daily. There are no dose adjustments needed for renal impairment or mild to moderate hepatic impairment (Child-Pugh Class A or B). Use is not recommended in severe hepatic impairment (Child-Pugh Class C).

Letermovir may also be given intravenously dosed 1:1 as to the oral regimen. The IV solution is compatible with polyvinyl chloride (PVC) bags, infusion sets, and radiopaque polyurethane catheters; however, letermovir is incompatible with polyurethane-containing IV tubing. With regard to compatibility, see Table 1 for a full list of bags and infusion sets. When compatibility testing was performed, IV line infusion sets with polyurethane tubing had a significant decrease in medication content measured by assay after 3 hours of static exposure; furthermore, an unidentified potentially leachable impurity was also found (Merck & Co., Inc, 2017).

ADVERSE EFFECTS

In the phase III trial, the frequency and severity of adverse events were similar between the le-

termovir and placebo groups. Any adverse event occurred in 97.9% in the letermovir group and 100% in the placebo group. Adverse events that occurred more frequently in the letermovir group are shown in Table 2. Myelosuppression was not seen in the letermovir or placebo groups (Marty et al., 2017).

ROLE OF ADVANCED PRACTITIONERS

Letermovir is the first and only FDA-approved medication for the prevention of CMV reactivation in seropositive patients undergoing a HCT. It is not myelosuppressive, which gives it an advantage over ganciclovir and cidofovir in a patient population in whom stem cell engraftment is desired; further, it does not cause renal impairment, which gives it an advantage over foscarnet. However, a cost analysis comparing prophylaxis of all eligible patients with letermovir prophylaxis as compared to monitoring of viremia with selective use of preemptive treatment of viremia with the aforementioned agents has not been reported.

The role of the advanced practitioner (AP) in CMV prevention begins with the screening process. The patient and potential donors are screened for CMV serostatus, where a seropositive donor is generally preferred for a seropositive recipient if possible. It is also important to select the most appropriate conditioning regimen considering all risks and benefits, as total-body irradiation and antithymocyte globulin can increase a patient's risk for CMV reactivation. Letermovir can impose a substantial cost to the patient; therefore, the AP can facilitate with the patient assistance process up front to alleviate this burden.

Another intervention that can be led by the AP is ensuring letermovir is prescribed and ini-

Table 1. Letermovir Infusion Compatibility

IV Bags	Infusion Sets	Plasticizers	Catheters
<ul style="list-style-type: none"> • Polyvinyl chloride (PVC) • Ethylene vinyl acetate (EVA) • Polyolefin 	<ul style="list-style-type: none"> • PVC • Polyethylene (PE) • Polybutadiene (PBD) • Silicone rubber (SR) • Styrene-butadiene copolymer (SBC) • Styrene-butadiene-styrene copolymer (SBS) • Polystyrene (PS) 	<ul style="list-style-type: none"> • Diethylhexyl phthalate (DEHP) • Tris (2-ethylhexyl) trimellitate (TOTM) • Benzyl butyl phthalate (BBP) 	<ul style="list-style-type: none"> • Radiopaque polyurethane

Table 2. Phase III Trial of Letermovir Prophylaxis for CMV in Hematopoietic Cell Transplant: Select Adverse Events

Adverse event	Letermovir (n = 373)	Placebo (n = 192)
Vomiting	69 (18.5%)	26 (13.5%)
Peripheral edema	54 (14.5%)	18 (9.4%)
Headache	52 (13.9%)	18 (9.4%)
Dyspnea	30 (8.0%)	6 (3.1%)
Myalgia	19 (5.1%)	3 (1.6%)

Note. CMV = cytomegalovirus. Adapted from Marty et al. (2017).

tiated at the appropriate time (i.e., within 28 days of HCT). Letermovir should be initiated only if CMV viral load is undetectable (i.e., viral load < 137 copies/mL). Since letermovir is currently approved only for prophylaxis, initiating the medication when the viral load is detectable introduces a risk of developing resistance to the medication. Throughout therapy, CMV viral load should still be monitored in patients receiving letermovir prophylaxis to assess for breakthrough viremia and determine if preemptive therapy should be initiated to prevent end-organ disease. Since there is not an established viral load threshold by which to begin preemptive therapy, having a standardized cutoff (or risk-adapted cutoffs) for the institution optimizes patient care. While there is not a renal dose adjustment for oral or IV letermovir, serum creatinine should also be monitored due to potential for accumulation of hydroxypropyl betadex, which is the IV vehicle. If the patient requires IV letermovir, the pharmacist should be contacted to make sure the IV tubing used by the institution is one of the compatible infusion sets (Merck & Co., Inc., 2017).

CONCLUSION

As many as 70% of allogeneic HCT patients can experience CMV reactivation. Historically, the approach to prevent end-organ disease was to monitor for viremia and begin preemptive therapy when viral load became elevated above a selected threshold. Currently, letermovir has been shown to be a safe and effective medication to prevent CMV reactivation in seropositive patients at risk of developing CMV-related morbidity and mortality while undergoing HCT. ●

Disclosure

The authors have no conflicts of interest to disclose.

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