Cytomegalovirus Viremia and Death After Hematopoietic Cell Transplantation: More Complex Than “To Have and Have Not”?

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(See the Major Article by Ljungman et al on pages 1525–33.)

Cytomegalovirus (CMV) has haunted the field of hematopoietic cell transplantation (HCT) since its inception. A major killer in the first 100 days post-HCT in the 1980s [1], CMV was tamed considerably in the 1990s with preemptive therapy, leading to a low incidence of CMV end-organ disease and directly attributable mortality [2]. Yet, it persists as a clear and present danger, threatening the wellbeing and survival of CMV-seropositive recipients [3, 4]. The challenge to mitigate the multifaceted consequences of CMV in transplantation has been a driving force in clinical virology, immunology, and drug development, and advances in these fields have led to our enhanced understanding of CMV. Establishing that asymptomatic CMV replication (expressed as viremia or DNAemia) correlates with CMV end-organ disease and death in HCT recipients enabled the use of CMV viremia (or the initiation of preemptive therapy) as a surrogate endpoint in clinical trials for the evaluation of CMV antivirals in HCT recipients [5].

The approval of letermovir by the Food and Drug Administration in November

2017 represents a remarkable achievement in many ways. After a hiatus of more than 2 decades in novel anti-CMV antivirals, letermovir is a first-in-class CMV-terminase inhibitor [6], is the first antiviral approved for CMV prevention in HCT recipients, and is the first antiviral to be approved based on the endpoint of clinically significant CMV viremia (cs-CMV-i), defined as the level of CMV viremia triggering the initiation of preemptive therapy by the treating clinician [7]. In the Phase III, randomized, placebo-controlled trial, letermovir was administered to CMV-seropositive recipients for the first 100 days post-HCT and significantly reduced the risk of cs-CMV-i at 200 days post-HCT, compared to placebo (18.9% vs 44.3%, respectively; $P < .001$) [7]. A prespecified exploratory endpoint of the trial was all-cause mortality. The correlation between CMV viremia and an increased risk of death was well established by retrospective registry studies and single-center cohorts [3, 4]. The Phase III letermovir trial showed—for the first time in a prospective, controlled setting—that modifying the risk of CMV viremia leads to improved survival. At 24 weeks post-HCT, all-cause mortality was lower among letermovir recipients than placebo recipients (10.2% versus 15.9%, respectively; $P = .03$). At 48 weeks, the trend for lower mortality among letermovir recipients persisted (20.9% vs 25.5%, respectively; $P = .12$) [7]. This finding has programmatic implications beyond CMV

prevention. Letermovir is not only an effective intervention for CMV prevention in the form of a safe and well-tolerated pill, but also has the potential of improving the survival of CMV-seropositive HCT recipients. The planned randomized study to extend the duration of letermovir prophylaxis to 200 days for high-risk patients will hopefully provide further insights on the potential of letermovir to provide a survival benefit beyond Week 48.

Albeit infrequently in the Phase III trial, cs-CMV-i occurred in some letermovir recipients, with the majority of events occurring after stopping letermovir, during weeks 15–24 post-HCT. The questions that arise are: (1) was the survival benefit among letermovir recipients linked to the reduction of cs-CMV-i or something else; and (2) did letermovir prophylaxis in any way benefit patients that did develop cs-CMV-i?

In this issue of *Clinical Infectious Diseases*, Ljungman and colleagues [8], address these questions by providing a post hoc analysis of the Phase III mortality data. Because the study intervention (letermovir) was an effect modifier for cs-CMV-i (the endpoint of the study), the authors further stratified the patients by the occurrence of cs-CMV-i by Week 24 post-HCT. Among patients with cs-CMV-i, letermovir recipients had lower mortality at 48 weeks, compared with placebo recipients (15.8% vs 31%, respectively; $P = .02$). In contrast,

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among patients without cs-CMV-i, mortality was similar between letermovir versus placebo recipients (19.4% vs 18.2%, respectively). In multivariate analyses, letermovir reduced the risk of death through Week 48 only among patients with cs-CMV-i (hazard ratio 0.45, 95% confidence interval [CI] 0.21–1.00; $P = .05$). In addition, cs-CMV-i through Week 24 remained a significant predictor of mortality (HR 2.58, 95% CI 1.69–3.92; $P = .03$), along with acute graft versus host disease GVHD and risk for CMV reactivation. Interestingly, at 48 weeks, the all-cause mortality rate for letermovir recipients with cs-CMV-i was similar to the mortality rate of recipients without cs-CMV-i. Reporting the causes of death, stratified by cs-CMV-i and letermovir vs placebo, might have been informative but was not done in this study. By what mechanism could letermovir exert its protective effect in patients who “failed letermovir prophylaxis”? The authors postulate that the later occurrence of cs-CMV-i among letermovir recipients may partially explain their findings. The majority of cs-CMV-i in letermovir recipients occurred after Week 14 post-HCT, in contrast to its occurrence in placebo recipients. It is plausible that earlier cs-CMV-i may require a longer duration of preemptive therapy and may incur more toxicities when the graft is more fragile. Unfortunately, no data are presented to corroborate this hypothesis.

In addition to the timing of the CMV infection, 2 factors that determine the response to preemptive therapy are (1) viral fitness and (2) host immune status. Ultimately, long-term control against CMV hinges on immune reconstitution, which, in turn, is linked to survival. The impact of letermovir exposure on viral kinetics merits further study. In a recent meta-analysis of viral kinetics during preemptive therapy, the maximum viral load and duration of viral load correlated with death [5]. In the letermovir Phase III trial, among patients with early cs-CMV-i

(by Week 14 post-HCT), 84% of letermovir recipients had the maximum CMV viral load of <1000 IU/mL, compared to 28% of placebo recipients, suggesting potential differences in viral load kinetics [7]. This may imply a potential effect of prior letermovir exposure to the virologic response to polymerase inhibitors.

The impact of letermovir on the tempo and magnitude of immune reconstitution also needs to be explored. In prior studies, in vivo priming and expansion of CMV-specific T cell precursors were hindered by ganciclovir prophylaxis [9]. In contrast to ganciclovir, letermovir may promote in vivo priming. Letermovir exposure has been associated with the cytoplasmic accumulation of large amounts of subviral, noninfectious particles (dense bodies), which have been evaluated as CMV vaccine candidates in preclinical studies [10]. Understanding the impact of letermovir on immune reconstitution, along with validated in vitro assays [11] to measure clinically meaningful CMV responses, may enable us to tailor the durations of prophylaxis to individual patients.

In summary, the study by Ljungman et al [8] makes the intriguing and provocative observation that letermovir prophylaxis in the first 100 days after HCT reduces the risk of death among patients who develop cs-CMV-i. Their findings open the door to more studies to understand the impact of letermovir on viral fitness, host immunity, and mortality, and, ultimately, to explore the potential of bridging the survival gap between CMV-seropositive and -seronegative recipients. Letermovir gives us a powerful tool to explore these and other questions in a real-world setting where it can continue to improve patients' lives and advance science by sharing experiences through registry studies or other means. While there will be challenges along the way, in 2020 the outlook is clearly positive for CMV-seropositive HCT recipients.

Note

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