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SUMMARY

CMV infection is a serious problem in hematopoietic cell transplant patients, leading to increased rehospitalization, longer length of hospital stay, higher treatment costs, and increased mortality. This most often occurs after antiviral therapy has been discontinued. Merck's Prevymis (letermovir), which was recently approved by the FDA for CMV prophylaxis, may help address these issues.

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CLINICAL AND COST BURDENS OF CMV AND ANTIVIRAL THERAPIES FOR HCT PATIENTS

For more than 25 years, preemptive antiviral therapy has been the standard of care for cytomegalovirus (CMV) infections in hematopoietic cell transplant (HCT) patients. These drugs typically have been IV Cytovene (ganciclovir, Roche) or its oral prodrug, Valcyte (valganciclovir, Roche), or, alternatively, IV Foscavir (foscarnet sodium, Clinigen) or Vistide (cidofovir, Gilead Sciences).

While prophylactically treating patients soon after HCT with antiviral therapy can reduce the clinical burden of CMV infection and improve outcomes, reducing CMV infection/ disease and mortality, antiviral use is associated with drug-specific toxicities, including myelosuppression (neutropenia or thrombocytopenia with ganciclovir, valganciclovir, and cidofovir) and renal toxicity (with foscarnet and cidofovir).[1] CMV preemptive treatments do not prevent most adverse *indirect* effects of CMV, including graft failure, acute and extensive chronic graft-versus-host disease, and bacterial and fungal infections.[2]

Studies presented at IDWeek 2017 in October 2017 examined the clinical and economic burdens associated with CMV following HCT and pointed to the need for new antiviral agents with an excellent safety profile to prevent the onset of CMV infections.

CMV Reactivation and Impact of Antiviral Therapies on Late Onset CMV Disease

The two most important risk factors for CMV disease in HCT recipients are (1) the serologic status of the donor and recipient, and (2) CMV reactivation. A large study using the Center for International Blood and Marrow Transplant Research (CIBMTR) database found that early CMV reactivation and CMV serostatus increased non-relapse mortality (NRM) with a resultant decrease in disease-free survival (DFS) and overall survival after HCT. CMV reactivation also did not seem to confer protection against hematologic disease relapse.[3]

Today, with the widespread use of preemptive ganciclovir therapy, the majority of CMV disease now occurs after the drug has been discontinued, between Day 100 and Day 270 after transplantation. One study found that late CMV disease developed in 17.8% of patients a median of 169 days after transplantation, with a mortality rate of 17% to 46%.[4]

Another study demonstrated that CMV reactivation requiring antiviral medications incurred a worse outcome and a significant cost when compared to a group that did not

receive preemptive therapy. In the first six months after transplantation, the group receiving therapy incurred longer hospitalization and additional costs for antiviral medication of $58,000 to $74,000 per patient.[5]

CMV-related Hospital Readmissions

A retrospective observational cohort study of 1,731 HCT recipients investigated the extent and impact of rehospitalization burdens caused by CMV and other infections. The majority of patients were treated in the inpatient setting with ganciclovir (62.7%), followed by foscarnet (39.1%) and valganciclovir (23.1%). Findings included:

- 212 recipients (13.7%) had ≥1 CMV-related readmissions during the 100 days post-HCT discharge.
- CMV-related rehospitalizations averaged 24.4 days, and the mortality rate during these rehospitalizations was 4.3%.
- Participants with at least one CMV readmission during the first 100 days post-transplant had a greater total readmission length of stay (31.9 vs. 13.0 days) and increased rate of mortality (31.1% vs 14.1%) vs. those without a CMV infection.
- The total costs of the first 100 days post-HCT discharge were more than twice as high for recipients who had a CMV readmission ($111,729 vs. $46,063).[6]

Need for a New Prophylactic Treatment Paradigm

For decades, the post-HCT treatment strategy has been to check the blood for the presence of CMV by various methods (such as shell vial culture, pp65 antigenemia, and DNAemia by PCR, with the latter being the standard of care in the U.S.) in asymptomatic patients, and if CMV is detected, to begin preemptive antiviral therapy. While prophylaxis for CMV is desirable in patients at risk, this strategy has not been feasible because of the toxicity of antiviral drugs. As far back as 2003, data suggested that preventing CMV infection might reduce long-term mortality rates more than expected.[4]

Three new anti-CMV compounds – Merck's Prevymis (letermovir), Chimerix's brincidofovir, and ViroPharma's maribavir have been studied in prophylactic clinical trials. Of the three, only letermovir met the primary endpoint in a Phase III clinical trial, and the FDA approved it November 8, 2017, for prevention of CMV infection in patients undergoing an allogeneic HCT.

In a multicenter study that treated patients with letermovir beginning within two weeks after HCT and continuing through Day 100 post-transplant:

- Significantly fewer patients with undetectable CMV DNA developed clinically significant CMV infections (defined as those requiring initiation of preemptive therapy) through Week 24 post-HCT (37.5% compared with 60.6% in the placebo arm).
- Letermovir prophylaxis also was associated with lower all-cause mortality through Week 24 post-transplant.[7]

Among HCT recipients, CMV infection is associated with high morbidity and mortality. It is a substantial contributor to the overall cost of HCT and a driver of increased healthcare resource utilization in the first 100 days post-transplant. Letermovir demonstrated it could safely prevent CMV infections in at-risk allogeneic HCT patients. Such antivirals may eliminate the myriad burdens of CMV infection or reactivation and its treatment. This development would represent a potentially game-changing paradigm in CMV management. ■

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