Session: O-05. Clinical Quandaries in Viral Infections in ICH

Background. Subclinical CMV reactivation on letemovir prophylaxis may be important for CMV-specific immune reconstitution after HCT (Zamora et al. Blood 2021) but concerns remain regarding the development of antiviral resistance. Here we analyze risk factors associated with breakthrough CMV infection on letemovir and describe the incidence of de novo letemovir resistance.

Methods. All CMV-seropositive, allogeneic HCT recipients who received letemovir prophylaxis from 10/2018-2020 were analyzed. Weekly proportions and cumulative incidences of CMV reactivation are shown in Figure 1. Nine of 15 patients with CMV reactivation had sufficient serum for letemovir resistance testing. One C325Y mutation was identified in an umbilical cord blood transplant recipient who developed 4 weeks of CMV DNAemia with a peak of 2512 IU/mL. The patient received 56 days of letemovir prior to reactivation and responded to treatment initially with foscarnet (due to cytopenias) followed by ganciclovir. Greater cumulative steroid exposure was associated with increased risk of CMV reactivation and the association remained statistically significant at any level (adjusted Hazard Ratio [aHR] 10.8 mg/kg*days, 95% confidence interval [CI] 5.18-22.7) and ≥ 150 IU/mL (aHR 15.9 mg/kg*days, 95% CI 7.07-35.6) after adjusting for underlying disease and GVHD prophylaxis (Table 2).

Results. Two hundred thirty HCT recipients who received letemovir prophylaxis were identified. Weekly proportions and cumulative incidences of CMV reactivation are shown in Figure 1. Nine of 15 patients with CMV reactivation had sufficient serum for letemovir resistance testing. One C325Y mutation was identified in an umbilical cord blood transplant recipient who developed 4 weeks of CMV DNAemia with a peak of 2512 IU/mL. The patient received 56 days of letemovir prior to reactivation and responded to treatment initially with foscarnet (due to cytopenias) followed by ganciclovir. Greater cumulative steroid exposure was associated with increased risk of CMV reactivation and the association remained statistically significant at any level (adjusted Hazard Ratio [aHR] 10.8 mg/kg*days, 95% confidence interval [CI] 5.18-22.7) and ≥ 150 IU/mL (aHR 15.9 mg/kg*days, 95% CI 7.07-35.6) after adjusting for underlying disease and GVHD prophylaxis (Table 2).

Conclusion. Letemovir prophylaxis was effective at preventing clinically significant CMV infection but subclinical reactivation continued to occur. Cumulative steroid exposure was the strongest risk factor for reactivation while on letemovir. Development of de novo letemovir resistance on prophylaxis occurred infrequently.

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21. Efficacy and Safety of Maribavir as a Rescue Treatment for Investigator Assigned Therapy in Transplant Recipients With Refractory or Resistant Cytomegalovirus Infections in the SOLSTICE Study: Phase 3 Trial Results

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Session: O-05. Clinical Quandaries in Viral Infections in ICH

Background. Refractory or resistant (R/R) cytomegalovirus (CMV) infection after hematopoietic cell transplant (HCT) and solid organ transplant (SOT) cause serious, potentially fatal complications; therapeutic options are limited. In a Phase 3 study (NCT02931539), maribavir (MBV) was superior to investigator-assigned therapy (IAT; val/ganciclovir, foscarnet, cidofovir) for CMV clearance (Wk 8) and clearance plus symptom control (Wk 8 through Wk 16) in HCT/SOT recipients with R/R CMV infections. Here we present further study results on efficacy and safety of MBV in the rescue arm.

Methods. Patients (pts) were stratified and randomized 2:1 to MBV (400 mg/bid) or IAT for 8-wk treatment then 12-wk follow-up. After minimum 3-wk treatment, pts in the IAT group meeting criteria (worsening/lack of improvement of CMV infection or failure to achieve viremia clearance plus IAT intolerance) could enter a MBV rescue arm (8-wk treatment, 12-wk follow-up.) In the rescue arm, efficacy was evaluated by confirmed CMV viremia clearance (CMV DNA < 137 IU/mL in 2 consecutive tests ≥ 5 days apart) at end of Wk 8 and confirmed clearance with symptom control at Wk 8 through Wk 16. Safety was assessed.

Results. A total of 352 pts were randomized (MBV: 235; IAT: 117, randomized set). Confirmed CMV viremia clearance at Wk 8 was achieved in 131 (55.7%) and 23 (23.9%) pts, respectively, in the randomized set. Having met criteria, 22 (18.8%) pts entered the MBV rescue arm; at entry, 6 (27.3%) pts had developed neutropenia and 9 (40.9%) had increased serum creatinine (Table 1). At Wk 8 of rescue therapy, 11 (50.0%) pts achieved confirmed CMV viremia clearance; 6 (27.3%) pts had confirmed CMV clearance with symptom control at Wk 8 maintained through Wk 16 (Table 2). All 22 pts reported treatment-emergent adverse events (TEAEs; Table 3); most common TEAEs of special interest were nausea, vomiting, and diarrhea (34.5%), and taste disturbance (50.0%). Neutropenia and acute kidney injury TEAEs were reported by 0 and 3 pts in the rescue arm, respectively.

Table 1. Summary of patients from IAT-randomized group meeting criteria for entry into MBV rescue arm

Table 2. Patients achieving confirmed CMV viremia clearance at end of Wk 8 (end of treatment) or achieving confirmed CMV viremia clearance and symptom control at end of Wk 8 maintained through Wk 16
Table 3. Treatment-emergent adverse events during the on-rescue observation period

| Subject | Any TEAE | Any treatment-related TEAE | Any TEAE due to treatment discontinuation | Any TEAE due to treatment discontinuation | Any TEAE that led to treatment discontinuation | Any TEAE that led to study discontinuation | Any TEAE that led to death |
|---------|----------|----------------------------|----------------------------------------|----------------------------------------|----------------------------------------|----------------------------------------|------------------------|
| MBV rescue arm | 22 (100) | 13 (59.1) | 1 (4.5) | 1 (4.5) | 1 (4.5) | 0 | 0 |
| MBV+IAT  | 31 (82.1) | 18 (46.2) | 3 (7.8) | 2 (5.1) | 1 (2.5) | 0 | 0 |
| Placebo rescue arm | 14 (73.7) | 10 (52.6) | 2 (10.5) | 0 | 0 | 0 | 0 |

**Results.** The total 4015 COVID-19 confirmed patients entered, we analyzed 3966 patients, 1115 cancer and 2851 non-cancer patients. Cancer patients were older than non-cancer patients (median age, 61 vs 50 years; p= 0.0001); more likely to be previously diagnosed with pulmonary disorders, hypertension and diabetes. In addition, they were more likely to present with higher inflammatory biomarkers (D-dimer, ferritin and procalcitonin), but were less likely to present with clinical symptoms. By multivariable logistic regression analysis, cancer was an independent risk factor for 30-day mortality (OR 1.46; 95% CI 1.03 to 2.07; p=0.03). Older age was a stronger predictor of 30-day mortality in all patients (OR 4.45; 95% CI 3.34 to 6.20; p< 0.0001). Remdesivir was the only therapeutic agent independently associated with decreased 30-day mortality (OR 0.58; CI 0.39-0.84; p=0.009). Among patients on low-flow oxygen at admission, patients who received remdesivir had a lower 30-day mortality rate than those transfused later (1% vs 7%; p=0.04).

**Conclusion.** Cancer is an independent risk factor for increased 30-day all-cause mortality from COVID-19. Remdesivir, particularly in patients receiving low-flow oxygen, can reduce 30-day all-cause mortality, as well as convalescent plasma given early after COVID-19 diagnosis.

**Abstracts • OFID 2021:8 (Suppl 1) • S15**