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Managing Refractory Cytomegalovirus After Hematopoietic Cell Transplant

Announcer:
You're listening to ReachMD. This medical industry feature, titled "Managing Refractory Cytomegalovirus After Hematopoietic Cell Transplant," is sponsored by Takeda.

Here's your host, Dr. Jennifer Caudle.

Dr. Caudle:
Welcome to ReachMD. I'm your host, Dr. Jennifer Caudle, and here with me today to talk about how we can manage refractory cytomegalovirus, or CMV for short, after hematopoietic cell transplantation is Dr. Amir Ali. He's an Adjunct Clinical Professor of Pharmacy Practice at the University of Southern California School of Pharmacy. Dr. Ali, it's great to have you with us today.

Dr. Ali:
Thanks so much for having me!

Question 1:

Dr. Caudle:
Sure. So if we start with some background, Dr. Ali, what do we need to know about CMV infection after hematopoietic cell transplantation?

Dr. Ali:
Well first, it's really important to know that 22,000 hematopoietic cell transplants, also known as HCTs, were performed in the United States in 2020.[1] But unfortunately, it's not uncommon for these patients to develop post-transplant CMV, which is a leading cause of morbidity and mortality after HCT.[2] These CMV infections can either be refractory, meaning there's a persistent viral load after at least two weeks of antiviral treatment,[3,4] or resistant, in which case there's a refractory *and* an altered viral genetic sequence that decreases susceptibility to one or more antiviral treatments.[3,4]

We also know there is a common risk factor for CMV is the need for immunosuppressants to treat acute or chronic graft-versus-host disease.[5] But the good news is that tremendous progress has been made since the first bone marrow transplant in the 1950s, thanks to advancements in immunosuppression, testing, and treatment of common complications.[6,7] In fact, according to a study conducted in 1986, the incidence of CMV and CMV end-organ disease was 51.4 percent and 16.7 percent, respectively.[8] But fast forwarding to 2017, a study found that the incidence of CMV dropped to 35 percent, and CMV end-organ disease was down to 4 percent, which is certainly a marked improvement.[1]

Question 2:

Dr. Caudle:
That certainly does sound like some important progress. And with that background in mind, let's examine refractory CMV after HCT through the lens of a hypothetical patient case. Can you share those details with us, Dr. Ali?

Dr. Ali:
Of course! So here we have a 40-year-old male with a history of refractory B-cell acute lymphoblastic leukemia who underwent haploidentical bone marrow transplant with a conditioning regimen of fludarabine plus melphalan and total body irradiation.

He received cyclophosphamide post-transplant, and he achieved engraftment on day 16. The CMV serostatus is donor negative, and recipient positive. He was started on letermovir CMV prophylaxis 5 days post-transplant. On day 40, his CMV viral load was 16,532 IUs per milliliter, and he was started on foscarnet 90 milligrams/kilograms twice daily.

But on day 41, the patient was admitted to the hospital with nausea, numbness, and diarrhea. He underwent upper and lower GI endoscopy, and his biopsies showed scattered CMV-positive cells within the lamina propria and glandular epithelium. At this point, he

was diagnosed with CMV colitis, stomatitis, and duodenitis.

He continued foscarnet treatment for 3 weeks. But on day 62, an infectious disease specialist was consulted for persistent CMV viral load around 2,400 IUs per milliliter, with new onset hemoptysis, hypoxia, and shortness of breath. His GI symptoms had improved, however.

Question 3:

Dr. Caudle:
So given those details, what options do we have available to treat this patient?

Dr. Ali:
Well, this patient has unfortunately developed refractory CMV infection despite treatment with foscarnet. And even though his genotype assay showed no mutations that conferred resistance to foscarnet, he was still refractory because his CMV infection did not respond to foscarnet.

So we could try treating him with ganciclovir, valganciclovir, or cidofovir, but we also have an alternative option called LIVTENCITY, or maribavir. LIVTENCITY is indicated for the treatment of adults and pediatric patients 12 years of age and older weighing at least 35 kilograms with post-transplant CMV infection or disease that is refractory to treatment—with or without genotypic resistance—with ganciclovir, valganciclovir, cidofovir or foscarnet.[9]

And I'd like to note that lab testing to confirm genotypic resistance to the current treatment is NOT needed before switching patients to LIVTENCITY. If a patient has CMV that is not responding to the current treatment and is considered refractory, then the patient may be a candidate for LIVTENCITY.[9]

Dr. Caudle:
Thank you, Dr. Ali. Now, let's take a moment to review some Important Safety Information for LIVTENCITY.

Announcer:
IMPORTANT SAFETY INFORMATION

Risk of Reduced Antiviral Activity When Co-administered with Ganciclovir and Valganciclovir

LIVTENCITY may antagonize the antiviral activity of ganciclovir and valganciclovir by inhibiting human CMV pUL97 kinase, which is required for activation/phosphorylation of ganciclovir and valganciclovir. Coadministration of LIVTENCITY with ganciclovir or valganciclovir is not recommended.

Virologic Failure During Treatment and Relapse Post-Treatment

Virologic failure due to resistance can occur during and after treatment with LIVTENCITY. Virologic relapse during the posttreatment period usually occurred within 4-8 weeks after treatment discontinuation. Some maribavir pUL97 resistance-associated substitutions confer cross-resistance to ganciclovir and valganciclovir. Monitor CMV DNA levels and check for maribavir resistance if the patient is not responding to treatment or relapses.

Question 4:

Dr. Caudle:
So now that we have that important safety information in mind and before we check back in with our patient, let's take a look at the clinical trial for LIVTENCITY. Dr. Ali, can you walk us through the study design and key endpoints?

Dr. Ali:
Yes, so SOLSTICE was a Phase 3, multicenter, randomized, open-label, active-controlled superiority trial in patients who received solid organ transplant or HCT.[8,9] It was designed to evaluate the efficacy and safety of LIVTENCITY versus investigator-assigned treatment, or IAT for short, which included one or two of the following conventional CMV antivirals: ganciclovir, valganciclovir, foscarnet, or cidofovir.[9,10]

Now in terms of the endpoints, the primary endpoint was confirmed CMV DNA level below the lower limit of quantification or LLOQ for short, meaning below 137 IUs per milliliter in two consecutive samples tested at least 5 days apart, at the end of week 8.[9,10] And the key secondary endpoint was CMV DNA level below LLOQ and CMV infection symptom control at week 8, with maintenance through week 16.[9,10] However, I'd like to point out that the clinical trial design had some limitations. Having clear, objective inclusion criteria and measurement of treatment time by necessity may not always reflect true clinical practice. The open-label design meant that blinding was not feasible due to the individualized IAT drug selection and dosing adjustments, with different administration compared to LIVTENCITY. The clinical trial enrolled only patients aged 18 and older. Additionally, the study was not powered to detect differences between treatment arms in patient subgroups, and patients were not stratified by refractory or resistant CMV at randomization. And finally, the study-specified treatment duration may have necessitated patients with residual CMV at the end of week 8 to receive alternative treatment, who were then classified as non-responders.[9,10]

As I mentioned only patients aged 18 and over were enrolled in the study. The use of LIVTENCITY in pediatric patients 12 years of age and older, and weighing at least 35 kg, is based on the following:

- Evidence from controlled studies of LIVTENCITY in adults

- Population pharmacokinetic modeling and simulation demonstrating that age and body weight had no clinically meaningful effect on plasma exposures of LIVTENCITY
- LIVTENCITY exposure is expected to be similar between adults and children 12 years of age and older and weighing at least 35 kg
- The course of the disease is similar between adults and pediatric patients to allow extrapolation of data in adults to pediatric patients

The safety and effectiveness of LIVTENCITY have not been established in children younger than 12 years of age[8]

So with all that in mind, the last thing I'd like to review is the baseline characteristics of the patients involved. The trial arms were balanced by multiple adult patient parameters and included several types of transplant. About 40 percent of patients had undergone HCT, while the other 60 percent received solid organ transplant.[9,10]

Now a range of CMV DNA levels at baseline were seen, though only 6 percent of patients in each arm had high levels. Intermediate CMV DNA levels, defined as those measured between 9,100 and 91,000 IUs per milliliter, were seen in 29 percent of patients in the LIVTENCITY arm and 21 percent of patients in the IAT arm. It's important to note that 65 percent of the LIVTENCITY group and 73 percent in the IAT group had CMV DNA levels below 9,100 IUs per milliliter.

Symptomatic CMV infection was seen at baseline in 9 percent of patients in the LIVTENCITY arm and 7 percent in the IAT arm. Among the symptomatic patients, 57 percent in the LIVTENCITY arm had tissue invasive disease, while one of the symptomatic patients, or 13 percent, had tissue invasive disease in the IAT arm at baseline.

And finally, the mean age of trial subjects was 53 years and most subjects were male, white, and not Hispanic or Latino, with similar distributions across the two treatment arms.[9]

Question 5:

Dr. Caudle:
So, Dr. Ali, now that we've reviewed the study design, what were the key findings of SOLSTICE?

Dr. Ali:
Well, in terms of the primary endpoint, 56 percent in the LIVTENCITY arm achieved CMV DNA level below LLOQ at week 8 versus 24 percent in the IAT arm,[9] demonstrating statistical superiority over IAT. Some patients who achieved CMV DNA level less than LLOQ experienced virologic relapse, also known as recurrence, during the follow-up period. In fact, after the end of the treatment phase, 50 percent in the LIVTENCITY group and 39 percent in the IAT group who achieved CMV DNA level below LLOQ experienced a virological relapse during follow-up, most occurring within 4 weeks of discontinuation.[9] However, this is to be expected; in the study, as secondary prophylaxis was not recommended during the 12-week follow-up period, so this doesn't reflect what often happens in clinical practice. Virological failure due to resistance can also occur during and after treatment. In the study, 34 percent experienced virological failure on LIVTENCITY versus 36 percent in the IAT arm due to not achieving CMV DNA level below LLOQ or CMV DNA breakthrough.[9]

Question 6:

Dr. Caudle:
And what about the secondary endpoint?

Dr. Ali:
The key secondary endpoint was also met, as a significantly higher proportion of patients on LIVTENCITY achieved CMV DNA level below LLOQ and symptom control at week 8 and maintained efficacy through week 16.[9] And in this instance, symptom control was defined as a resolution or improvement of tissue-invasive disease or CMV syndrome for symptomatic patients at baseline, or no symptoms in patients who were asymptomatic at baseline. These patients were considered responders.[9]

In both treatment arms, the percentage of patients achieving the composite endpoint was lower than the primary endpoint due in part to virologic relapse. This reflects the latent nature of CMV infection when virus may reactivate in periods of immunosuppression.[10] And response in subgroups related to treatment and disease characteristics was consistent with the responses observed in the primary analysis or randomized overall population of adult patients with refractory or resistant CMV.[9,10]

Virologic resistance to LIVTENCITY was observed in the study follow-up period. In patients with phenotypic resistance to valganciclovir or ganciclovir, DNA sequence analysis of the entire coding regions of pUL97 and pUL27 was performed on paired sequences from 134 LIVTENCITY-treated patients. Treatment-emergent pUL97 resistance-associated substitutions, or RAS for short, was detected in 58 patients; 47 of them were on-treatment failures, meaning non-responders to the primary endpoint, and 11 were relapsers.[9]

And lastly, in terms of cross-resistance, pUL97 RAS reduced susceptibility to LIVTENCITY by more than 4.5-fold. Some substitutions in pUL54 conferred cross-resistance to valganciclovir and LIVTENCITY, and those who developed resistance during the trial were still being treated with foscarnet.[9]

Question 7:

Dr. Caudle:
Thanks for breaking all of that down for us, Dr. Ali. And with that data in mind, let's go back to our patient case. What steps were taken

to treat him, and how did he fare?

Dr. Ali:
Well, on day +62, he was prescribed oral LIVTENCITY at 400 milligrams twice daily. Then, on day +75, his CMV viral load decreased to 177 IUs per milliliter. He was no longer short of breath on room air and was discharged.

During the trial treatment phase, the patient was seen on routine follow-up and had no evidence of CMV pneumonitis. His CMV disease and viremia improved, and he experienced mild dysgeusia but no other symptoms.

On day +110, his CMV viral load was less than 137 IUs per milliliter at the end of treatment. There was no more evidence of CMV end organ disease or CMV reactivation. And on day +194, which was the last day of follow-up while on protocol, he had a viral load less than 137 IUs per milliliter and no evidence of ongoing CMV infection or end organ disease.

Question 8:

Dr. Caudle:
Thank you for sharing that patient case and how LIVTENCITY can be used for post-transplant refractory CMV. Now what about LIVTENCITY's safety data and recommended dosing? What do we need to know there?

Dr. Ali:
Right, this is interesting to note because there was a lower rate of treatment discontinuation due to adverse events with LIVTENCITY versus IAT.[9] In the LIVTENCITY arm, 13 percent of patients discontinued due to adverse events; the most common events at 1 percent each were taste disturbance, diarrhea, nausea, and recurrence of underlying disease,[8] while in the IAT arm, the discontinuation rate due to adverse events was 32 percent. The most common events were neutropenia at 9 percent and acute kidney injury at 5 percent.[9]

And here we can see the adverse events, of any grade, that were reported in >10% of adult patients for LIVTENCITY. Taste disturbance was the most common adverse event reported in the LIVTENCITY arm. Patients in the LIVTENCITY arm had similar rates of nausea at (21%), diarrhea at (19%), vomiting at (14%), and fatigue at (12%).[9] As I mentioned earlier, the patient from our case experienced taste disturbance, and this is consistent with the LIVTENCITY arm of the trial, as 46 percent of the 234 patients experienced dysgeusia. Taste disturbances rarely led to treatment discontinuation though, and resolved in 37 percent of patients while on treatment and in 89 percent of patients post-treatment.[9,10]

In terms of dosing, the recommended dose is 400 milligrams in the form of two 200 milligram tablets twice daily for adults and children 12 years and older weighing at least 77 pounds.[9] LIVTENCITY can be taken as whole, dispersed, or crushed tablets by mouth, or as dispersed tablets through a nasogastric or orogastric tube. Please refer to the full prescribing information for more details. Dose adjustments are needed if LIVTENCITY is co-administered with certain anticonvulsants, but no adjustments are needed for patients with mild, moderate, or severe renal impairment nor mild or moderate hepatic impairment.[9]

Lastly, there are drug-drug interactions with immunosuppressants, antiarrhythmics, and antimycobacterial to be aware of.[9] And if we go back to our patient case one last time, he was on the immunosuppressant tacrolimus, but his drug levels were monitored frequently throughout treatment, especially after initiation and discontinuation.[9]

Question 9:

Dr. Caudle:
Now, unfortunately, we're almost out of time for today, but before we close, Dr. Ali, what key takeaways would you like to leave with our audience?

Dr. Ali:
So although refractory CMV is a leading cause of morbidity and mortality after HCT,[1] LIVTENCITY is an effective treatment option for post-transplant refractory CMV per the data from the SOLSTICE trial.[9,10]

Dr. Caudle:
Thanks for summarizing all of that for us, Dr. Ali. And as that brings us to the end of today's program, I'd like to thank my guest, Dr. Amir Ali, for helping us better understand LIVTENCITY as a treatment option for patients with refractory CMV after hematopoietic cell transplantation.

Dr. Ali, it was great speaking with you today.

Dr. Ali:
It was a pleasure being here. Thank you, Dr. Caudle.

Dr. Caudle:
For ReachMD, I'm your host, Dr. Jennifer Caudle. Please stay tuned to hear Important Safety Information for LIVTENCITY.

Announcer:
Important Safety Information (continued)

Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions.

- The concomitant use of LIVTENCITY and certain drugs may result in potentially significant drug interactions, some of which may lead to reduced therapeutic effect of LIVTENCITY or adverse reactions of concomitant drugs. Consider the potential for drug interactions prior to and during LIVTENCITY therapy; review concomitant medications during LIVTENCITY therapy and monitor for adverse reactions. Refer to the full prescribing information of LIVTENCITY for important drug interactions.
- Maribavir is primarily metabolized by CYP3A4. Drugs that are strong inducers of CYP3A4 are expected to decrease maribavir plasma concentrations and may result in reduced virologic response; therefore, coadministration of LIVTENCITY with these drugs is not recommended, except for selected anticonvulsants.

Use with Immunosuppressant Drugs

LIVTENCITY has the potential to increase the drug concentrations of immunosuppressant drugs that are CYP3A and/or P-gp substrates where minimal concentration changes may lead to serious adverse events (including tacrolimus, cyclosporine, sirolimus and everolimus). Frequently monitor immunosuppressant drug levels throughout treatment with LIVTENCITY, especially following

initiation and after discontinuation of LIVTENCITY and adjust immunosuppressant dose, as needed.

Adverse Reactions

The most common adverse events (all grades,> 10 percent) in subjects treated with LIVTENCITY were taste disturbance, nausea, diarrhea, vomiting, and fatigue.

Announcer:
This program was sponsored by Takeda. If you missed any part of this discussion, visit ReachMD.com, where you can Be Part of the Knowledge.

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