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Are You Failing Your HCT Recipients? A Case Study on CMV Prophylaxis

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Are You Failing Your HCT Recipients? A Case Study on CMV Prophylaxis” is provided by Prova Education and is supported by an independent educational grant from Merck.

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Dr. Chemaly:
This is CME, and we are ReachMD, and I’m Dr. Roy Chemaly.

Dr. Perales:
And I’m Dr. Miguel Perales.

Dr. Chemaly:
Together, we’ll be reviewing the practical applications of new data in CMV management in HCT recipients through case-based scenario. So without further ado, Dr. Perales, let’s dive right into the details of our patient case. AR is a 61-year-old female who underwent allogeneic HCT transplantation three days ago as part of her management for acute myeloid leukemia. The match unrelated donor was CMV seronegative; however, they are CMV seropositive. Now, Miguel, this is a typical scenario. So why are so many patients still not receiving prophylaxis with letermovir?

Dr. Perales:
That’s an excellent question, because we now have randomized data, as well as FDA approval of letermovir in this indication. And so, as you know, letermovir was studied in a randomized phase 3 trial compared to placebo in patients undergoing allogeneic stem cell transplant. The patients were treated for a duration of 14 weeks with letermovir, and the primary endpoint was CMV reactivation at 24 weeks after transplant. And what that study showed is that the patients who received letermovir had a significant reduction of CMV reactivation at 24 weeks, the primary endpoint. And this is the first study in the prophylaxis era to show a difference at that time point. In addition, the secondary endpoint also showed the decreased overall mortality, which I think is also important from the transplant perspective because obviously anything we can do to improve outcomes and decrease mortality is a significant advance. Now let’s break down the study a little bit. The study was stratified by patient risk groups and so the investigators would find patients who were at standard risk and high risk. And high risk included patients who were recipients of cold blood, mismatched unrelated donors, or T-cell deficient. And the rest of the patients were considered standard risk. The study was positive in the whole cohort, but it was also positive in patients both in the standard-risk group, as well as the high-risk group. And that’s most important in terms of how we think about implementing this in practice. And just to put some numbers around that, in general, the risk of CMV reactivation is probably estimated around 40 percent with a standard risk population, but can be as high as 80 to 100 percent in these high-risk patients such as cold blood or ex-vivo T-cell depletion. So what have people been doing prior to letermovir? The approach was similar to CMV 4:16 with a

PCR, and then used preemptive therapy. So the numbers I gave you in terms of reactivation are a factor of the preemptive therapy. With prophylaxis, we've seen a significant reduction in CMV reactivation, so that really should be considered the standard of care today. Why are centers still somewhat reluctant to embark on prophylaxis? I think some of it has to do with the fact that it's a new drug, some centers don't have experience with it in the setting of the clinical trial, and then some would see it as a cost associated with this. Because I think it will be important for us to see some cost-effective analysis comparing prophylaxis to preemptive therapy. But let's get back to the case now. Let's imagine that the patient is undergoing stem cell transplant and now has an early CMV reactivation. How would that typically be handled?

Dr. Chemaly:
Thank you, Miguel. And I would like to add also this is interesting what the phase 3 trial for letermovir versus placebo for prevention of CMV, infection after allogenic transplant showed the signal about all-cause mortality, which was lower in – for patients who received letermovir. and I think this is also was reflected in other studies. One of them was the CIBMTR, study published around a few years ago looking, – tried to ask the same question, which was: Does CMV reactivation increase all-cause mortality, versus patients who don't reactivate? And after they looked at 9,000 and – almost 9,500 patients in this database, they found the same, evidence or signal that any CMV reactivation after allotransplant in patients who had underlying leukemia, all-cause mortality was higher in patients who had CMV-positive viral load or CMV reactivation versus the ones who did not. And this – these patients were all CMV seropositive. So I think it's interesting we're seeing more and more covert kind of studies versus the phase 3 trials for letermovir showing all of the same impact on all-cause mortality. I think this is really interesting to mention and to talk about.

Dr. Perales:
I agree that those are important studies, because connecting the dots between viremia, CMV disease, as well as all-cause mortality is critical because that really tells us that we can use CMV reactivation as a surrogate endpoint. And what the phase 3 study showed is that we showed a benefit from CMV viremia, and we also showed a benefit in all-cause mortality. And as you know, there was a recent publication in CID in October, which further looked at data from the phase 3 trials. And in that study, they specifically looked at patients with clinically significant reactivation and those without. And what struck me in that paper was that the patients with clinically significant reactivation had again a benefit in terms of mortality if they were treated with letermovir versus placebo. Whereas, a patient who didn't have clinically significant CMV reactivation, we didn't see that difference. So it really shows that CMV reactivation and the ability to suppress that with letermovir is – is a critical finding from this phase 3 trial and it has an impact on all-cause mortality. Um, so getting back to the patient that we mentioned earlier, this patient with AML undergoing an allogeneic stem cell transplant, what would you do if this patient reactivated CMV about eight days out from her transplant?

Dr. Chemaly:
Yeah. So this is interesting. As we start to see, sometimes early reactivation within day 15 or day 30 after transplantation, especially now when we are doing more molecular testing. So we're looking at CMV viral load by PCR or other molecular testing, which are pretty sensitive tests. So when we start looking for CMV early on, we're finding some high-risk patients may have a, CMV reactivation. Now the question, always is, is it significant or not? Do we need to treat or not? Our approach, at least in my institution, if you have a lower level of reactivation, below a certain threshold that we define in our institution where it puts patients at risk for progression, if it's below the threshold, we may not treat. We may not stop letermovir, especially if the patient is already on prophylaxis letermovir. We continue the drug; it's only small blurb, it's below the level of, the threshold of what we call clinically significant CMV infection. we repeat the viral load three, four, or one week later. And if we see a steady increase, then we'll stop letermovir, we treat with commercially available anti-CMV drugs. or if it goes back, to negative or still on the low, side with low level of reactivation, we'll continue letermovir. So this has been our recommendations, especially after we've been experiencing with letermovir for almost two years now. so we don't jump the gun and stop letermovir and start therapy unless the viral load goes above a certain threshold. And there's different thresholds depending on the patient, the risk factors for CMV reactivations. If we define the patient having high – being at high risk for CMV reactivation and the viral load is above, for us at least at MD Anderson, above 500 IU, or international units per mL, then we start treatment. If patient is low risk, any viral load above 1,000 IU/mL, then we'll start, preemptive what we call preemptive therapy. And then probably later on we can discuss more risk factors that define patients or stratify patients into low risk and high risk.

Dr. Perales:
We have adopted very much a similar approach at Memorial in terms of how we manage patients on letermovir. I think this is something that as you embark on prophylaxis at your center critical to understand that seeing some reactivation doesn't mean that you have to stop. And actually we published our data already, with a paper that was written by Andrew Lin published last year in Journal of Infectious Diseases, which shows exactly what I just described.

Dr. Chemaly:
No, absolutely. I completely agree. And I would like to add also, that because we start seeing that early reactivation, and we start

checking for CMV early on I think it's paramount to start letermovir as early as possible. I don't want to wait until day 14 or day 30 when we may miss some 12:56 reactivated, and now they have progression of their CMV viral load, and they won't be eligible for letermovir. This is why we decided to start as early as day 5, at least in our institution, and I know also many institutions probably like yours Miguel, that you're starting early on. We don't want to miss the boat for the high-risk patient where they can have early reactivation.

Dr. Perales:
So that – the study allowed patients to start up to almost a month post-transplant, but I think all the evidence suggests that the earlier you start, the better, and so very much like you're saying that at Anderson where you start within the first week, that's also the strategy we've adopted. And I think the centers that have adopted letermovir have all adopted earlier administration because that's what the data supports.

Dr. Perales:
Alright, so I think the duration of treatment is also going to be interesting. Because now we'll have data for 100 days. We're going to be doing a study comparing 100 days to 200 days. But those are somewhat arbitrary endpoints. And I think what would be really useful to the clinician is to have some sort of test that could tell them, you know, it is now safe to stop prophylaxis. And do we have any data to help guide, you know, should the patient receive 100 days, 150 days, 200 days, or more? What are your thoughts on that?

Dr. Chemaly:
Yeah, yeah, absolutely. Actually, so it's interesting now as there is good data already published looking at CMV specific T-cell responses after transplant. You know, either early on, later on, after day 100. And when you mentioned early on, Miguel, is the duration may be off prophylaxis. If someone at day 100 or day 90 they still have no specific or neuroblasts, CMV specific T-cell response, maybe this patient needs to be continued longer on prophylaxis until their immune system recover better and now they have more T-cells, to protect them from CMV reactivation in the specific T-cell.

Dr. Chemaly:
Well, this has certainly been a valuable conversation. And before we wrap up, Dr. Perales, can you share with our audience any take-home messages from our discussion?

Dr. Perales:
Well thanks. For me, the take-home messages are really we now have randomized data supporting the use of CMV prophylaxis with letermovir. There is also an all-cause mortality benefit. This drug should be given both to what we consider standard-risk and high-risk patients. So really any patient who's at risk for CMV reactivation should receive prophylaxis. and we've seen now in the real-world experience from our center and from your center and other centers that the drug in the real-world experience is performing similar to what we saw in the clinical trials. In fact, the results may even be better because I think we're now, at least in the clinical setting, tolerating these very low levels of CMV activation, and maintaining the patients on letermovir prophylaxis, whereas in the clinical trial, those patients will have been considered a failure and will have been switched to preemptive therapy at that time. But I think there are still things we need to learn about the duration of prophylaxis, but I think prophylaxis is the standard of care in 2020.

Dr. Chemaly:
We waited for more than 20 years to have a safe drug available in the oral format to prevent CMV. And I think we now have letermovir that filled one of the gaps we had in managing CMV infection after allogeneic cell transplantation. Unfortunately, that's all the time we have for today. So I want to thank you, Dr. Perales, for joining me and for sharing all of your valuable insight. It was great speaking with you today.

Dr. Perales:
Thank you. And I very much enjoyed our conversation, as well.

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Chemaly_Perales

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[SC1]Help

[SC2]Help