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Combating CMV in HCT Recipients: A New Era of Therapy

Announcer:
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Dr. Mencia:
This is CME on ReachMD, and I’m Dr. William Mencia. Joining me to discuss the importance of CMV preventive strategies in patients receiving hematopoietic cell transplantation is Dr. Roy Chemaly. Dr. Chemaly, welcome to the program.

Dr. Chemaly:
Thank you.

Dr. Mencia:
So, Dr. Chemaly, we know that data shows us that after allogeneic transplant, the risk of activation or reactivation and infection can be anywhere between 30 and 80% depending on a series of different factors. What are some of those factors that determine a recipient’s risk for CMV infection?

Dr. Chemaly:
Yeah, so, many patients after allogeneic stem cell transplantation are going to be at risk for CMV activation, which may lead to CMV disease or what we call end-organ disease. Number one risk factor, actually, the recipient serostatus for CMV, if the recipient been previously exposed to CMV and they have, they are also CMV seropositive, this is a major risk factor determinate for the risk for reactivation of CMV after transplant, but there is also many other risk factors that we look for either at baseline – we may look at the donor’s serostatus because there’s some data showing that if the donor is seronegative for CMV, the risk for recipient after transplant could be a little bit higher than if the donor is seropositive. There is also other baseline risk factors like the type of transplant, if we’re talking about match unrelated donor transplantation or haploidentical, or the source of the cells could be cord blood cell transplant. These are other risk factors all determinate of the risk of CMV reactivation. Now, this is not, it is a dynamic issue where it’s not only baseline characteristic which will certify patient at low risk or high risk for CMV activation, not only that, but also over time after transplant, after day 30 or engraftment when patient may get graft-versus-host disease, which is one of the major complications after allogeneic transplantation, this is another risk factor because these kind of complications could be treated with steroids. It could be a pretty high dose or lower dose, depends on the site and the extent of GvHD. This is another risk factor that comes into play later on after transplantation.

Dr. Mencia:
So, because of these many risk factors, CMV is still quite prevalent. So, what continues to keep you up at night when you think about CMV infection, and what progress have we made over the last 5-10 years?

Dr. Chemaly:

Good question, actually. So, for more than 20 years, we realized that CMV infection and CMV end-organ disease could be quite common after allogeneic transplants, especially if the risk, mainly when the recipient is seropositive for CMV, and if you think about it, this is probably one of the most common infections that we may encounter after transplantation, if, you know, in this patient where up to 80, sometime 90%, of these patients may have some kind of CMV reactivation or infection, could be quite significant, especially when it leads to CMV end-organ disease. So, for many, many years, we tried to see what the best strategy either to prevent or to mitigate this kind of complication after transplantation. When we had some new drug on the market more than 20 years ago, like ganciclovir, later on foscarnet, then valganciclovir, for example, we start using these drugs to try to see, as a prophylactic tool after transplantation, but we find out, you know, early on that these drugs can cause serious side effects. So, using them on these patients at risk for prophylaxis for a long time or longer duration may not be the strategy to do because of the serious toxicities from these medications. I will give you an example for the ganciclovir – myelosuppression – it is quite common, and for foscarnet – nephrotoxicity as well – as well as for cidofovir. So, we shifted away from prophylaxis strategy to preemptive strategy, and what I mean by preemptive strategy or preemptive therapy is when we start having a good sensitive test to look for CMV in the blood or plasma either by molecular testing, or in the past we used to do CMV antigenemia. So, patients were followed on a weekly or twice-weekly, twice-a-week basis where we checked for CMV even without any symptoms, but we take blood from patients, we run these tests, and if it is positive before patients become symptoms or before they progress to end-organ disease, we treat these patients with the available drug at that time for therapy, which is ganciclovir versus foscarnet, and this way we have been exposing patients, hoping to expose patients to only short durations of these toxic drugs to treat for early reactivation short time period, then stopping the drug, but unfortunately with this strategy, it does not prevent further episodes down the road where patients who are at risk, they're going to continue to be at risk, and they may get more than one episode of CMV reactivation, but what we accomplish with this preemptive strategy, actually, the incidence of CMV end-organ disease went down, was reduced because we were catching this infection early, although we still were seeing some toxicities of these drugs that we use for treatment of preemptive therapy, and this had been going on for more than 20 years until recently, around two years ago, when one new agent called letermovir was FDA approved for CMV prophylaxis in adults who after allogeneic transplants are CMV-seropositive, you know, and to prevent CMV infection or what we call clinically significant CMV infection. So, I will talk more about letermovir, how it changed the way we approach CMV after allogeneic transplantation and how it changed the incidence of even CMV reactivation.

Dr. Mencia:
As I also understand it, there are some therapies that have currently been under investigation in late-stage clinical trials that maybe unfortunately have not produced the types of results that we hoped – one being brincidofovir – and actually one that may be producing some positive results is maribavir. What can you tell us about this agent?

Dr. Chemaly:
Yes, so for many years I've been involved with clinical trials, many clinical trials, from phase 2 through phase 3, for new agents to prevent CMV reactivation or infection after allogeneic transplant, starting first with maribavir. If I remember, it was the first drug that we tested in phase 2 trial. It was a positive, you know, result that prevented more CMV reactivation than placebo, but we moved on to phase 3 trial, and unfortunately for many of these instances could be the primary implement that we picked at that time versus the dose of maribavir, it was a negative trial. So, it failed as a drug for prevention of CMV reactivation after allogeneic transplant, but the good news, and I'm happy to see that the development of this drug, maribavir, continues, but mainly for treatment of CMV or resistant CMV infection to the other commercially available drugs. The phase 2 trial completed, already published, which showed that up to 67 or 70% of patients with the refractory or resistant CMV infection responded to maribavir, but also it's been developed for preemptive therapy. Someone who have early-on reactivation, they, you know, maribavir was used, and it worked nicely. In one of the trials, it was an open-label, dose-escalation trial, and these patients, and our patient population, also, and organ transplant, and the data were published just recently in New England Journal of Medicine. This was for maribavir, so I'm happy to see that it has been, the development is continuing, and now we have two phase-3 trials – one for refractory or resistant CMV infection and the second one for preemptive therapy for CMV reactivation – and we need to stay tuned, and we're hoping we may see some of the results hopefully in the near future, maybe in one year or so, and we're hoping that we can get another drug to the market where it would have a value in treating CMV when it's needed in this patient, in our patient population. Now, the other drug, also, which I have a good experience with as I was involved in the phase 2 and phase 3 trials as well for CMV is brincidofovir, which is a prodrug of cidofovir but has many advantages to cidofovir where it can be given orally. It had the lipid chain, side chain to cidofovir and does not have a major toxicity for the kidneys at least, but unfortunately we found out in the phase 2 and phase 3 trial that brincidofovir can cause GI toxicity or gastrointestinal toxicities, mainly diarrhea but could be also nausea and vomiting, and probably because of these significant toxicities of the GI tract that the drug failed to show effectiveness or efficacy in the phase 3 trial compared to placebo for CMV prophylaxis in adults after allogeneic transplants who were CMV-seropositive. For brincidofovir, also, the good news – its development was put on hold recently – but now, to my knowledge, a different sponsor or company is going to take over this drug, and they want to continue developing this brincidofovir,

but we're still under discussion for what indication and which virus because the main advantage of brincidofovir, I would say, is its broad spectrum of activity against almost all double-stranded DNA viruses.

Dr. Mencia:
So, Dr. Chemaly, let's switch gears back to our discussion on letermovir. We know that recently the European Conference on Infections in Leukaemia strongly recommended the use of letermovir for the prevention of CMV in adults with allogeneic hematopoietic cell transplantation. What can you tell us about the profound implications this change will make in our patients?

Dr. Chemaly:
I think this is very important, that, you know, and profound implication for our allogeneic transplant recipients. This is the first time that we have a drug like letermovir, which showed efficacy and good safety profile to prevent CMV reactivation in adults who are CMV recipient positive after allogeneic transplant, and I know that European guidelines that came out of ECIL recommended it as a, you know, A1 recommendation for prevention of CMV, and this is based on the phase 2 and phase 3 trials which were published recently.

Dr. Mencia:
So, it sounds like, Dr. Chemaly, that these guidelines are being updated to take into account the data that has been coming out of the clinical trials regarding letermovir as well as maybe some of the real-world experiences that we're seeing. What do you think are the practical implications of this medication based on the results of these clinical trials?

Dr. Chemaly:
Yeah, so, this drug – letermovir – first let me start by saying – it has a different mechanism of action than the available drug that we have that treats or prevents CMV infections. Its mechanisms of action work, actually, the way it works, it inhibits the terminase complex of CMV, so its viral-directed agent, it does not have a host target. So, this terminase complex, it is specific to CMV – UL89, UL56, and UL51 – and what it does when it inhibits the complex, you stop the elongation of DNA and then the packaging of DNA into procapsids, capsids, then virions and the virus. So, this is completely different mechanisms of action of other commercially available anti-CMV drugs where ganciclovir works on UL97, and at the end the product is still inhibit DNA polymerase as well as foscarnet directly on the DNA polymerase as well. So, this is one point I want to make, and this is the implication of that actually when you think about resistance to any of the other drugs – there is no cross-resistance to letermovir.

Now, let's talk a bit about the clinical trial. As I mentioned earlier, we were involved in the phase 2 and phase 3 trial where we were looking at prevention of CMV reactivation or what we call clinically significant CMV infection after transplantation, after allogeneic transplant in adults who were CMV-seropositive. In the phase 2 trial, we showed efficacy and superiority to placebo, and it was, we didn't not see any safety signals or events or any serious safety events that we could, you know, identify, and for that reason, actually, it moved on to phase 3 trial where more patients would enroll on this trial. The randomization can occur before engraftment, and this is very important because, based on the phase 2 trial, we didn't not see any signals of myelosuppression or delay in engraftment when we used this drug or any impact on engraftment when we used this letermovir in allogeneic transplant. So, we allowed randomization and started the study drug before engraftment, and I'm happy to say that out of almost 63, up to 67% of patients who received the study drug before engraftment, and why it is important because at least now we have strong evidence that had no impact on engraftment, no delay in engraftment, and no myelosuppression that we could see if patients received letermovir. So, this is an important point I want to make, and now, also, based on many previous trials with other drugs for prevention of CMV after transplantation, we learned that the primary endpoint in the paths that we use, which is CMV disease, it is not, doesn't make sense to use it in new trials because the incidence of it, it's down, actually, and reduced based on preemptive therapy. So, what we came up with is the definition of clinically significant CMV infection as a primary endpoint in the new trials that we did for CMV, especially with letermovir. So, the primary endpoint changed over time based on published data and based on communication with the FDA, also the European agency as well where it was acceptable to use this primary endpoint for the phase 3 trial, which is clinically significant CMV infection, but also what we came up with in the design, that this primary endpoint should be tested at week 24, meaning around 10 weeks after stopping the study drug. So, usually patients get randomized early on after transplant to study drug, and they will continue the study drug up to day 100 or week 14 from transplant, but the primary endpoint is measured around, actually, at week 24 to see if there is any carry-on effect of preventive therapy after stopping the study drug, and this is where the primary endpoint was measured.

Now, first, again to the endpoint as well as experiment to the endpoint, we added all-cause mortality, and this is important because there is nice data that I will share with you about all-cause mortality at week 14, actually, at week 24, as well as week 48. So, based on the phase 3 trial results, what we found was that patients who received letermovir either at 480 mg once a day if they were on tacrolimus or 240 mg once a day, or half of the dose, if they were receiving cyclosporine for prevention of graft-versus-host disease, they received this drug up to day 100 or week 14 from transplant, and what we found that it prevented, it was superior to placebo at week 14 as well

as week 24 where it prevented more clinically significant CMV infection than the placebo. So, it was a positive trial, which was great, but in addition to that, what we found when we looked at the exploratory endpoint, which is all-cause mortality at week 24, actually we found that more patients on the letermovir arm had survival advantage than the placebo arm or less all-cause mortality at week 24 and was statistically significant at week 24, and it continued until week 48, but it lost its statistical significance but numerically was higher all-cause mortality on placebo than patients being on, who received letermovir, and this was at week 48. So, I think for us it was kind of icing on the cake, actually, which was actually kind of a signal, turning out that if you prevent clinically significant CMV infection by using letermovir, you may see less all-cause mortality at week 24 and even at week 48. So, based on all this data, this drug letermovir was approved by the FDA and later on by the EMA, and by the FDA, actually, it was around November 2017 and was made available commercially for us to use it around January and February 2018.

And to talk a little bit about our real-life experience: Probably we were one of the first centers to start using letermovir as…

So, I would like to talk a little bit about our real-life experience with letermovir. We decided as a group with our transplanter and the infectious disease group to use, to start using letermovir at day 5 after transplant because the reason we want to start early, to make sure we're not missing the highest-risk patients where the reactivation can occur early on after transplant. So, we decided to do it around day 5 on all patients who are CMV-seropositive or recipient virus CMV-seropositive but with the caveat that they have to have an insurance clearance before we start using it on the inpatient because we want to make sure when they get discharged, on discharge, they will be able to get it if they got the approval from their insurers. So, this was, actually, our SOP at that time, and that's what we started doing it around early March 2018, and since that time until today, we have been using letermovir for to prevent CMV reactivation, and we went back and looked at our experience with letermovir because I want to make sure – Did it make a difference on our patients? And was the impact of using it because, as you know, a clinical trial is much more controlled environment, and you see sometimes good data, but we could be missing something else. So, we want to make sure and confirm that whatever happened at the phase 2 trial, that's what we see now with patients, and this was true, actually. When we went back and looked at around 129 patients, most of them received letermovir. Some of them did not because of insurance clearance and other issues or other reasons. We found the impact of CMV was the same as in clinical trial, meaning that it prevented more CMV reactivation than patient not being on letermovir, but what is more important, also, what we found out, is that we're having much less complications from CMV or we're seeing much less refractory or resistant CMV reactivation even after transplant when we start using letermovir. So, I would say it's a real paradigm shift when we start using letermovir where we're not seeing much of CMV reactivation. It's much less than before, than prior of letermovir approval, and we're not seeing severe cases of CMV infection or even end-organ disease.

Something else I want to underscore, which are the safety profile of this drug as well. As I mentioned earlier, we didn't see any safety signals or issues in the phase 2 or the phase 3 trial, and also we're keeping a close eye on these patients, and our experience with the drug, you know, the safety profile is as good as what we showed in the phase 3 trial and the phase 2 trial. What our providers need to keep an eye on? That's what we saw in the phase 3 trial – a little bit more of tachycardia or atrial fibrillation in patients who receive letermovir. We're not sure what to make out of it. When we look more into these patients who got these side effects of, or this cardiac side effect, these patients had prior cardiac conditions. So, I'm not sure if this is probably the reason or not, but something to keep in mind when we use letermovir for prevention of CMV reactivation after allotransplant.

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

Dr. Chemaly:
Yeah, absolutely, actually. So, for 20 years or more, we've been asking for a safe and effective drug or agent or strategy to prevent CMV infection, and this is based on our experience with the prior drug that we had for years based on their toxicities, and now, I think, with letermovir, we achieved one of the goals where we identified and we have a commercially available drug, which is safe and effective to prevent CMV reactivation but at the same time with some signals to reduce even all-cause mortality. So, I think this is a great accomplishment after many trials with different agents or strategies to mitigate the impact of CMV after transplant. As I mentioned earlier, I think it's going to be – it is a paradigm shift in the way we approach CMV after transplantation.

Dr. Mencia:
Well, with those take-home messages in mind, I want to thank you, Dr. Chemaly, for sharing all of your valuable insights throughout this discussion. It was great speaking with you today.

Dr. Chemaly:
Thank you. Thank you for all these questions as well, and thank you for the opportunity to share with you our experience with how to mitigate CMV complications after transplantation.

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