Novel Approaches to Treating CMV Infection in People Receiving Solid Organ or Hematopoietic Stem Cell Transplantations

CMEO Podcast Transcript

Roy F. Chemaly, MD, MPH, FIDSA, FACP:

Hello, I'm Dr. Roy Chemaly. I'm a professor of medicine, the chief infection control officer, and director of clinical virology research program in the Department of Infectious Disease at the University of Texas, MD Anderson Cancer Center in Houston, Texas.

On behalf of CME Outfitters, I would like to welcome you to today's educational activity title, novel approaches to treating CMV (cytomegalovirus) infection in people receiving solid organ or hematopoietic cell transplantations. Today's program is supported by an educational grant from Takeda Pharmaceutical USA Incorporated. Today's activity is brought to you by CME Outfitters, an award-winning, jointly accredited provider of continuing education for clinicians worldwide.

Let me now introduce our faculty. Joining me today is Dr. Genovefa Papanicolaou, or known as Dr. Zenia Papanicolaou. She's an attending physician in the infectious disease service at Memorial Sloan Kettering Cancer Center, and professor at Weill Cornell Medical College and Cornell University in New York, New York. Welcome Dr. Papanicolaou.

Genovefa (Zenia) Papanicolaou, MD, FIDSA:

Hello, Roy, and thank you for inviting me. It's a pleasure to be here today.

Roy Chemaly:

Thank you. I'm going to start with the learning objectives for today's activities, which are first identifying factors that increase the risk of CMV infection. Second, recognize the impact of CMV infection on treatment outcomes for transplant recipients. And lastly, develop balanced treatment plan for patient with CMV infection or disease.

Before we get to the exciting new data regarding the treatment of CMV infection, I would like to review with our learners the incidents, and the risk factor for CMV infection, and the impact of this on our patient. Let's start first with the incidents of CMV infection, and reactivation, and the burden of it in our HCT (hematopoietic stem cell transplant) or SOT (solid organ transplant) recipient.

Zenia, I will start with you. Can you tell me a little bit about the incidents first, and the impact that you see in all your patients?

Genovefa Papanicolaou:

Thank you, Roy. I see stem cell transplant patients, and of course the stronger risk factor is a CMV zero positivity of the recipient. And so, the incidents probably ranges between 40% and 80%, or more, with the lower incidents in much related donor graphs that are unmanipulated. And the highest incidents in the highest mismatched grafts, such as cord transplants, haploidentical donors, or grafts that have been manipulated to remove T-cells. So, T-cell depleted grafts, or those that have received T-cell depleted agents.

Roy Chemaly:

Okay, yeah. And as we know, so I think, Zenia, probably the most common, and the significant complication after either SOT or, the HCT recipient, especially in recipient positive, at least for the HCT group, and in donor positive recipient, negative for the solid organ transplant.

Now, with the CMV organ disease, actually, now these days, it's not that common. Although, it's still happening, it could be up to 6% an autologous transplant, or even 30% sometimes an allogenic hematopoietic cell transplant recipient, but with the preemptive therapy or prophylaxis, which we'll talk about it a little bit later on. This incidence is now less than 10% I would say. Maybe around 6% for either group.

What we worry most about CMV, it is not only the direct effect of CMV I would say on our transplant recipients, which is usually an organ disease. Because you can start with CMV activation, and then progress to an organ disease, meaning pneumonia, it may go to the lungs, or gastrointestinal disease, when it goes to the i-tract, causing colitis, causing esophagitis, or even gastritis.

Now, what about the indirect effect, Zenia, that you can little bit enlighten us, which we really worry about because of the CMV being the immunomodulator virus.

Genovefa Papanicolaou:

Exactly. And it is about this indirect effect that we believe that actually survival of the CMV zero positive patients is worse than the survival of CMV zero negative patients, even with preemptive therapy strategies. And we believe that part of this discrepancy is due to indirect effects.

In the stem cell transplant population, which I am more familiar with, CMV has been associated with a graft versus host disease, increased fungal infections. And those perhaps could be either related to immune modulation, or related to myelosuppression and neutropenia due to a valganciclovir treatment.

Now, in the solid organ transplant population, our colleagues have shown, of course, that the transplanted organ is more sensitive to being infected by CMV, but also they see allograph rejection, they see an increased risk of vascular disease, and atherosclerosis after heart transplant, and also some other comorbidities, including diabetes after renal transplant, which I'm not sure if this is related to immunosuppression or whatever. But certainly for sure, CMV infection is associated with increased hospitalization and increased costs.

Roy Chemaly:

Yeah, absolutely. We touch up a little bit about the risk factors for CMV infection. Let's start with the hematopoietic cell transplant recipient. What do you think will be the main risk factors that we look at that can predict probably CMV infection, disease in our HCT recipients?

Genovefa Papanicolaou:

The strongest predictor is of course zero positivity on of the recipient in the stem cell population. Because it is really the endogenous CMV that reactivates after transplant. And we can think about risk factor for CMV as a continuum. In the early peri-transplant period, the other additional predictors would be the type of donor. And as we said, that much related donor transplants had the lower incidents.

This zero positivity of the donor, so for CMV positive recipients as CMV zero positive graft confers some protection due to CMV specific T-cells procured by the graft, of course, conditioning regimens, regimens that have more T-cell depleting activity are at higher risk, and the general level of immunosuppression. For example, heavily pretreated patients, patients with malignancies are at higher risk, even if they get much related done or transplants.

Now later, from day 30 to 100, the biggest risk factor of course is graft versus host disease, and its treatment, particularly corticosteroids. And beyond the 100 days is really the immune reconstitution is driving the risk for CMV. If there is delay in T-cell recovery, then of course the patient remains on at risk, and we can see late CMV infections.

Roy Chemaly:

Yeah. Now, this is a great summary. And I know we know this is different in organ transplant recipient where patients receiving lung, the heart, and multi-organ transplant had the highest risk. Kidneys usually have the lowest risk. But the biggest risk factor also in this patient population for CMV disease is serological mismatch between the donor and the recipient. Recipient being zero negative, and donor zero positive probably the highest risk for this patient after transplantation of having CMV infection, CMV disease as well. And late onset CMV infection may develop up to third of the zero positive recipients as well. This is very nice summary of the risk factors.

Now, additional risk factors of CME infection, SOT, intense immunosuppression, same thing, probably HCT, as well acute rejection. Because at that time, you have to increase your immunosuppression. Same thing in HCT where you have graft versus host disease when your immunosuppression going to go up, you're going to put them on high dose steroid as well in this patient when they get this kind complications, I would say.

Now, let's move on. Talk a little bit about CMV diagnosis. We know we've been able to attack CMV for a long time, but there is several ways to do that. Can you walk us through a little bit of different diagnostic assay that you've been doing, Zenia, at your institution at least?

Genovefa Papanicolaou:

Yeah, sure. First, we start with CMV serology, so checking IgG. And this testing starts really before transplant to enable risk stratification. And actually, CMV infection is the only infection, to my knowledge, that drives also donor selection. If we have a CMV zero negative recipient, we try to find a CMV zero negative donor, and vice versa in the unmanipulated graphs, if we have a CMV zero positive recipient, we strive to find a positive donor. Providing of course that there are comparable HLA matches in the donor.

Now, after we have determined if the patient is CMV zero positive or zero negative, we need to be able to monitor for CMV replication, right? Because CMV replication is something that for sure we need to treat, and to prevent a disease, and other adverse events downstream. And so for that, we have now molecular quantitative assays. PCR (polymerase chain reaction) is the most common assay used throughout the United States, at least.

And the advantages of PCR is that is the turnaround time is fast, and provide really a quantitation. So, you know if the patient responding to therapy, if the patient has cleared his virema, and so that's quite useful. But CMV PCR doesn't tell us anything about the immune status of the patient, the ability of the host to control CMV. And there is where we have the CMV specific T-cell immunity assays, which have not been yet used as a routine standard of care, but it's a very exciting field where you can actually assess the present of CMV specific T-cells, and thus perhaps the ability of the host to control CMV.

Roy Chemaly:

Yeah. And I agree, I think it still have a role, too. It has a role in our management of CMV infection, and we try to identify exactly when this tool or extra test will help us at the bedside, taking care of this patient. Especially with this highly sensitive molecular test that we have, and we have detectable CMV, in the plasma or whole blood, do you need to treat or not? Perhaps CMV specific T-cell assays can lead us or help us to determine treatment or no treatment, or even stopping prophylaxis, or putting someone on secondary prophylaxis after a course of treatment for CMV infection.

We touch up a little bit about preventive strategies, and we know we have two type of strategies, right? We have either prophylaxis, or preemptive therapy. And the difference between the two prophylaxis that you put someone on a CMV drug or agent during the high-risk period, when they are at high risk for CMV activation, these patients you identify by risk factors. You put them on this drug to prevent CMV reactivation.

Preemptive therapy, actually the difference is you monitor CMV in the blood, by molecular assays usually, because you want sensitive tests. And if it is positive, you start treatment. And you start treatment for short period of time. As soon as they become negative, you go back to preemptive therapy, or to monitoring again. This is the two different between the two.

But there is a pros and cons between the two strategy. Can you tell us a bit, Zenia, about what really counts between the two. Why prefer maybe another strategy versus another one, at least in hematopoietic cell transplant recipients?

Genovefa Papanicolaou:

We think of these strategies really as a complementary. Preemptive strategy of course has the advantage of preventing completely CMV application, or clinically significant CMV application, and that's alleviating the need for a preemptive therapy. That even with preemptive therapy sometimes, we have a development of resistant or refractory CMV. We can still see some CMV disease, and we can still see some mortality, albeit rare these days.

Now, with prophylaxis, of course we prevent CMV application hopefully until the patient's immune system is strong enough to control CMV on their own. And of course, that hinges on the recovery of CMV specific T-cells. And the con of the prophylaxis is that you need to provide treatment to all patients at risk, and as you would actually give treatment to more patients than they actually would reactivate.

Now of course, with high-risk patients that their incidence of reactivation is so high, providing prophylaxis, it's not a very big leap, right? If normally 80% of your patients would need preemptive therapy, then providing prophylaxis is just an incremental, just a smaller increment.

With preemptive therapy, of course you target a treatment to only patients that need it, so that have active CMV replication. Unfortunately, with preemptive therapy, we have to deal with toxicities, particularly with the drugs that we had until recently. Namely ganciclovir and foscarnet. Ganciclovir and its oral drug, valganciclovir cause frequently neutropenia, particularly when they're given early after transplant, or when they are given for prolonged time. It's a dose dependent neutropenia, and it's up to 30% in certain series or higher.

With foscarnet, if neutropenia develops, or if patients cannot receive ganciclovir for any reason, because they are refractory, too, our alternative has been foscarnet. And that also is extremely cumbersome to give. It's given intravenously. It requires very intense monitoring, and replacement of electrolytes, and causes kidney injury.

Thankfully, we do have a newer therapy, which we're going to talk about. But until very recently, these were the two drugs that we had, and these are the disadvantages. And of course, if you have refractory CMV to any or both of these drugs, the alternatives were extremely limited or non.

Roy Chemaly:

Yeah, I totally agree, and this is interesting. Now, an SOT recipient, the approach are flipped actually. Because our colleagues who care for our solid organ transplant recipient been using prophylaxis for long period of time. And I think the reason is because we know that we have an available oral drug, which is valacyclovir, the pro drug for ganciclovir, that could be used on the outpatient for prevention of CMV or prophylaxis, CMV infection.

And so, the organ transplant, where in this patient, we don't worry much about neutropenia. They don't have a weak grad that we see in hematopoietic cell transplant recipient. Although, we know that the incidence of neutropenia could be high enough to stop the drug, but it is probably a little bit better tolerated in our SOT recipient patient than HCT, for sure.

Roy Chemaly:

But we know also there is a hybrid approach. Starting with prophylaxis, then you can go to preemptive therapy. And all with the struggle I think based on what I hear from our colleagues for prevention of CMV and SOT recipient is what the duration of prophylaxis as well, or even preemptive therapy. Are we delaying CMV activation? Because then, as soon as you stop your preventive strategies, are you going to start seeing CMV disease or not? The durations keep on increasing over time in order to prevent this serious complication after a solid organ transplant, same like in HCT as well.

Now, we talked about treatment, about prevention. Let's talk about the drug, the drug that either we have it, they've been on the market for a long period of time, and the new one that were recently FDA approved for CMV infection, either prevention or treatment. First, as you see in the table here, we have different drugs against CMV. We had different mechanism of action. And this is important because we always worry about cross resistance.

For letermovir, which works specifically on the terminus complex of CMV, UL56, UL89, and 51, it's an oral drug, but it's available also intravenously. It is approved for adults whom after stem cell transplant, who is recipient zero positive, and for prevention. Here, we're talking about the first drug actually been approved for more than few decades to prevent severe activation after hematopoietic cell transplantation, at least in renal. And has different mechanisms of action of the available drug.

Now, ganciclovir, valganciclovir , foscarnet, even valacyclovir, they actually they target the CMV . This is the end product, what they do. You can imagine with this drug, you may get cross resistant. If you have specific mutation to one drug, it may also give resistant to the other drugs as well. And then, yeah, you talked about the limitation of using this drug because of toxicities actually that we've been experiencing for many years now, using this drug to treat either preemptive therapy, as a preemptive therapy, or even resistant and refractory CMV infection.

Now, the last drug that was recently approved around, now it's been a few months ago, which is maribavir, it also has a specific mechanism of action. We'll talk about it later on more, but it's an oral drug, and it is specifically approved so far for adult patients actually, age 12 and above, for treatment of CMV infection which is resistant or refractory to conventional therapy that we've been using for years.

We know there's limitation of CMV treatment for the drug that's been available for years, maybe toxicity. You talked about myelosuppression, for ganciclovir and valacyclovir, nephrotoxicity for foscarnet, or even cidofovir as one. What we need to keep in mind the drug-to-drug interaction for letermovir probably, and we'll touch up on side the effect of maribavir later on.

Can you tell me a little bit, Zenia, about refracture and the refractory and resistant CMV infection, and really how we define it? Because we have to make sure we are all on the same page, especially in clinical trials. In outcome research studies or epidemiology study, are we comparing apple to apple or oranges to oranges in this patient population when we talked about refractory and the resistance of the infection?

Genovefa Papanicolaou:

Yeah. Thank you, Roy. And you, of course, spearheaded this effort, along with other colleagues, to really provide definitions that have been extremely useful for clinical trials, and comparing outcome. Let's start with resistant CMV infection that is a little bit more clear. The not so resistant is the presence of specific mutations that confer resistance to one or more anti-CMV drugs.

Now, that is not sufficient though. You also have to have a lack of clinical response to be defined as resistant. Refractory CMV infection is a term that was actually generated out of our clinical experience. That there are some patients where despite appropriately dosed antiviral therapy for at least 12 weeks, they do not have a virologic response. On the contrary, their CMV viral load continues to increase. And for the purposes of clinical trials, I think the definition is more than one log increase in viral load after two weeks of appropriately dosed antiviral therapy. This is the definition of refractory, and of course resistant is the addition of known resistance mutation, conferring resistance to one or more drugs.

Roy Chemaly:

Yeah. And yeah, and as we all know as well, Zenia, that refractive's probably much more common than resistance, right? Especially in HCT recipient where we all face at the bedside with challenging CMV infection where with the absence of mutation, you still patient don't respond to the available drugs as well.

Let's move on. Talk a little bit about the risk factors for resistance in CMV. We know there's host factors that they can put patient at risk for resistant CMV infection. Profound immunosuppression. We know that even when we dose the antiviral in suboptimal doses, and the reason we do it sometime to limit the toxicities. This can put patient at risk for developing CMV resistance. Have been poor compliance with preemptive therapy as well, or even poor absorption. These are the risk factors that can put patient at risk for CMV resistance.

Now, viral factors, initial high viral load we know from few studies that if you start with very high viral load, you can predispose patient to resistant CMV infection. And has to do with the viral replication candidates as well. And we looked at mutations, as you mentioned earlier, by doing genotypic analysis to see which patient we going to fail therapy because they have specific relation to a specific drug, which confer resistance to these drugs as well.

Now, we know that as common mutation, non-mutations, or what we call canonical mutation that confers anti-resistence in patients after hematopoietic stem cell transplant , but also the same mutation probably in solid organ transplantation. Letermovir works on the terminus complex. Most of the mutation that we see conferring resistance going to be on your L56. Maybe some on your LAT9. And you see listed here, there's many mutations that are confirm to provide resistant, or to confer resistant to CMV.

Maribavir works on L97, as we mentioned earlier, and specific mutation on your N97 confers to maribavir. But, what I want to caution everyone is there is specific mutation where on your L97 can confer resistant to both Maribavir and ganciclovir, or valganciclovir. Same thing for ganciclovir and foscarnet, there is specific mutation confer resistant to both, or even to cidofovir. You have triple a hit here. Specific mutation where you can get resistance to ganciclovir, Valcyclovir, foscarnet, and cidofovir as well.

Roy Chemaly:

Now, let's move on, and talk a little bit about the new approved drug, which is maribavir for treatment of resistant and refractory CMV infection. Zenia, can you tell us a little bit first about the mechanisms of action of maribavir, and the data behind phase two trial that I know you led a few years ago looking at tried to treat resistances and refractory CMV infection in hematopoietic cell transplant, and solid organ transplant recipients.

Genovefa Papanicolaou:

Thank you, Roy. Yes. I'm very excited to speak about maribavir. We've been having clinical trials for maribavir for the last 20 years almost, so it is exciting to finally have it for clinical practice. Maribavir also has a novel mechanism of action, unlike the known drugs for treatment of CMV does not target DNA polymerase. The target of maribavir is UL97, but it has a multimodel mechanism of action, and it prevents CMV in three ways. It prevents CMV replication, CMV encapsidation, and nuclear export of the viral capsid. A very interesting mechanism of action.

Initially, in the phase two study, which was a smaller study of course than the phase three, and open labeled, but patients were randomized to three different doses of maribavir, because it was also a dose finding study and enrolled patients with resistant and refractory CMV, which were either solid organ or hematopoietic cell transplant, in that study, 67% of the patients achieved undetectable CMV at six weeks, and all doses performed equally. For instance, the 400 BID, the 800 BID, and the 1200 BID. And this is something that we have seen in prior trials of maribavir, that there is not a dose response curve.

Now, these patients were heavily pretreated. And about one fifth, 20% of the patients had recurrence of CMV on treatment, and of those that developed a CMV breakthrough on treatment, about half had mutations conferring maribavir resistance. Again, this was a phase two trial, and the patients were very heavily and very prolonged treated before going into maribavir. And after all, maribavir was discontinued at about one third of the patients, and at about half was due to CMV infection.

Overall, I think it was a very positive trial in this very sick population. And of course, this trial led to the design of the phase three trial that you are very well familiar with.

Roy Chemaly:

Yeah. Yeah, and you're right, Zenia, that this patient, when they enter this trial, they had very complicated course of CMV infection, and very challenging for us, and they were heavily treated. And seeing this result actually make us really very hopeful, at least in the phase two trial, to move it to this phase three trial, that maribavir worked very nicely in this very complicated cases of CMV infections and disease as well.

Yeah, based on the phase two trial result, we move to the phase three trial, which is the sources trial, phase three randomized open label trial where maribavir at 400 POBID, or twice a day was compared to investigator assigned therapy, which could be, again, aciclovir, valganciclovir, foscarnet, cidofovir, or even combination as well.

Roy Chemaly:

In this trial actually, patients were randomized two to one to either maribavir versus IAT, which is the investigator assigned therapy, and the primary input in this trial was the confirmed CMV clearance on two occasion, five days apart, of negative CMV in the plasma at week eight. This is the primary endpoint of the trial.

Now, we had a key secondary endpoint as well, which is CMV clearance, but also symptom control both at week eight, but if they were maintained until week 16 of follow up as well. Let's dive in a little bit, and show you the result of the trial. And first for the primary endpoint, we see that maribavir performed much better than the IAT, which is investigator assigned therapy. Around 56% of patient on maribavir had met the primary endpoint with CMV clearance at week eight, versus only 23.9% or 24% of patient on IAT at the difference of 32.6%, which is adjusted difference, which was statistically significant as well.

Now, Zenia, can you tell us a little bit about the key secondary endpoint? Which is also very interesting data in this phase three trial.

Genovefa Papanicolaou:

Yes. The secondary endpoint was clearance and symptom control at a later time point. And I believe it was at week 16. And as you can see, of course, less patients maintained this endpoint, but still more patients in the maribavir arm met this secondary endpoint compared to the investigator assigned therapy.

And of course, we need to remember that what is the substrate of these patients? And the substrate of these patients are heavily immunosuppressed. And if the immunosuppression persists after the treatment phase, which was eight weeks, of course it is predicted that you are going to see some late infections of the assigned therapy.

Roy Chemaly:

No, yeah. This is very good point. Because we tend to forget that this patient who had this kind of infection, which is resistant or refractory infection, and so when you stop the studied drug or the drug to treatment, and they are still going to have recurrent infection. And it's always happened, even in preemptive therapy, even patient with no refracture and resistance, as soon as we know, as soon as we stop preemptive therapy, they may have another episode of CMV infection.

It's not only one episode and that's it. We're done with it. These patients are still at risk. They're going to have multiple episode. And that's what we saw in the sources trial, but still when you confirm maribavir, as you mentioned, to IAT, it was the rate or recurrence, it was much lower than the IAT I would say.

And this would take me to the clinically relevant recurrence of CMV during follow up period. After you stop the study drug, it was lower on the maribavir 28%, versus almost 37% on the IAT. This was not unexpected actually. That's why now we talk about secondary prophylaxis all the time. If this patient is still at risk for a recurrent infection, they probably need to go on secondary prophylaxis.

Now, let me ask you a question about the specific population, or the subgroup analysis that were done in the trial. Can you tell us a little bit about the difference between maribavir and IAT arms?

Genovefa Papanicolaou:

Right. This was a first kind of a trial in the sense that it included solid organ transplants, and stem cell transplants. We don't get the chance frequently to work with our SOT colleagues. And so of course, one question is whether maribavir worked well in both transplant populations, and indeed it worked almost equally well in the solid organ and stem cell population.

And again, in every subgroup that was looked at, whether it was by the type of the investigation assigned, of assigned therapy, by transplant type, by the baseline viral load, or by baseline resistance to other antivirals, maribavir performed equally well in every subgroup. Very important.

And one thing I want to point out is that when for the patients that had documented resistance mutations, maribavir performed better, of course, because maribavir addressed really the heart of the problem, the presence of mutations to other drugs. Overall, in all subgroups, maribavir performed better than the investigator assigned therapy.

Roy Chemaly:

Yeah. No, absolutely. Now, let's talk a little bit about maribavir safety, and this was very important during the trial to look at the safety. And what I want to tell the audience mainly is that the most common side effect probably for maribavir is dysgeusia. And we knew this for years, actually. If you remember, while, Zenia, when we used the drug for prevention of CMV long time ago in a different trial, dysgeusia was also one of the main common side effects.

But what is important and interesting had no impact, that there were no side effect related to myelosuppression, or acute kidney injuries, or what we call renal dysfunction, or other serious side effect. Especially when you compare it to IAT or investigator assigned therapy where the rate of neutropenia for was much higher, and the rate of, or the incidence of kidney dysfunction was much higher for patients who received foscarnet on this trial.

I would say at least we know that maribavir, it is safe, and does not cause serious side effect. Even for dysgeusia, less than 1% of this patient who had dysgeusia discontinued the study drug of maribavir during the trial. It was only two patient, if I remember, who discontinue maribavir because of dysgeusia while on this trial. Still even with dysgeusia, it is most of the time very well tolerated, and patient can sail through it when you treat the infection. This is the main safety profile of maribavir.

Now, let's move on to the recently published guidelines. Actually, Zenia, that you led, along with other colleagues and myself for the American Society of Transplant and Cellular Therapy for treatment options for refractory CMV infection. I know at that time when we put all this together, maribavir was not approved, and we didn't have the final result of the sources trial. But we mentioned in the guidelines that it could be an option, but we could not grade it as an option to treat recent infection, because it was prior to its approval.

Now, in retrospect, let me ask you, would you see that maribavir should be a first line therapy for recent refractory CMV infection, at least after hematopoietic cell transplantation in this patient population?

Genovefa Papanicolaou:

Yeah, absolutely, Roy. I think that we were at a race, because we wanted to get the guidelines out. And maribavir was at the late stages of approval, so we could not really recommend it with the evidence. But certainly after the FDA, and the European counterpart regulatory approvals, maribavir should be first line for treatment of resistant and refractory CMV.

Roy Chemaly:

Excellent. Thank you.

Now, let's talk a little bit about our own experience. I would say we took us more than 20 years, if not more, to get to this point where now we have two safe and effective drug to manage CMV infection. First, letermovir. We all know for the past now it's been four to five years where it was approved for prevention of CMV infection. And about after allogeneic transplantation for prevention. And we know the real world data looks pretty good. Now recently, maribavir.

Let me ask you, what's your experience with maribavir? What are you doing at Memorial Sloan Kettering when it comes to recent refractory CMV infection in your patient population?

Genovefa Papanicolaou:

Roy, as you know well, letermovir is used at our institutions for CMV prevention. The resistant and refractory CMV that we see is much less than we used to see with preemptive therapy, and you have very beautifully showed that in your recent publication in CID (Clinical Infectious Diseases). However, we do see some CMV infection, particularly in patients that have discontinued letermovir, and have a need for immunosuppression, or delayed immuno recovery.

And there are circumstances that we have used maribavir in situations where the patients cannot use ganciclovir. If you remember also in the clinical trial, there was a rescue arm that you could switch to maribavir if you developed toxicity from the investigator assigned therapy.

This is a little bit off the label that says just resistant refractory CMV, but certainly I believe that patients that are intolerant, or develop toxicity from ganciclovir or valacyclovir, we have used maribavir in these situations. Or that patients that cannot really receive ganciclovir due to neutropenia.

Roy Chemaly:

Yeah. And this is our own experience as well, same as yours, where over the past few months, we used it at least on six patients who needed maribavir because they have refractory and/or resistant CMV infections. And we have great result as well. Hopefully, we're putting all this together. Actually, at least try to share our experience with the real world usage of maribavir.

Thank you, Zenia, for the very interesting discussion, and your input on this very complicated infection after transplantation. And let me start wrapping up a little bit.

Roy Chemaly:

Today, what we did, we discussed CMV infection as a significant problem after HCT and SOT as well. And we know recipient zero positive for HCT are the main risk factors for CMV infection, and donor zero positivity and recipient zero negativity are the major main risk factor for SOT recipients as well.

Now, we have different strategy, the prophylaxis preemptive therapy. We have the hybrid approach for SOT recipient as well, and refractory as well resistant remain a challenge for us. We know that this is unfortunately a situation that we're going to be seeing as we go, and we need to address it. And we are hopeful now that we have a safe and effective drug, which is maribavir, to treat this complicated infection after transplantation in SOT or HCT recipients as well.

I would like also to leave the audience with some small goals, which are specific, measurable, attainable, relevant, and timely. First, review patient and transplant characteristics in order to identify patient higher risk for CMV reactivation and/or disease. Request genotyping, or genotypic analysis when you suspect resistant or refractory CMV infection, but maybe consider letermovir for CMV prophylaxis in patient after allogeneic hematopoietic stem cell transplant, and the right indication. And consider maribavir for treatment of resistant refractory CMV infection, or disease in patient receiving either HCT or SOT, because indicated for both patient population.

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And again, thank you, Zenia, for your input, and the discussion. And thank you to our audience also for joining us today.

