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Navigating CMV Post-Transplant: Perspectives on Complex Cases: A Clinical Forum®

Announcer:
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Dr. Chemaly:
Good morning. Yeah, it looks like the microphone is working. Thank you.

Good morning everyone, and thank you for joining us today. It's a great way to start ID Week Meeting with a symposium on CMV. Great way to start. And let me start with the introduction first. I'm Roy Chemaly. I'm a Professor of Medicine and the Chair of the Infectious Disease Department at MD Anderson Cancer Center in Houston, Texas. I'm joined today with Dr. Atul Humar. He's a Professor of Medicine at the University of Toronto and the former Director of the Transplant Institute in Toronto.

It's going to be a comprehensive kind of symposium where you're going to hear about hematopoietic cell transplant in CMV, and solid organ transplant in CMV — mainly difficult-to-treat cases of refractory and resistant CMV infections.

So let's start first. I'm going to start to go over CMV in the stem cell transplant world, and after me, Dr. Humar will talk about CMV in SOT.

I would like to start with this famous quote: “CMV is my favorite virus. But make no mistake, CMV is not my friend.” Anyone knows who said that? Raise your hand if you never attended one of my lectures. Actually, it was me, around maybe a few years ago. And the reason I like to start with this is to tell you how fascinating CMV really is. For years and for decades, we've been studying it, and we didn’t even scratch the surface about how CMV really works and how it affects our immune system. We’ve learned quite a bit about it, but still, there’s so much to learn about it.

But you know, we know how bad it is when it happens to our patients. Even having latent infection—meaning being you know exposed and dormant without reactivation—can affect stem cell transplant outcomes and SOT outcomes. So this is why it makes it so—you know—so bad as a virus, but also a very fascinating virus.

So and these are the consequences of CMV in HCT recipients. And this will sum up many of the more higher complication risks. We know if the recipient is positive, or if you have CMV viremia, you’re going to get into trouble after transplant. It may cause tissue-invasive disease. We used to worry much about progression from viremia to end-organ disease, but it’s not only that — this the direct effect. What about the indirect effect? It may predispose to bacterial, fungal, and viral infections, make the outcome worse.

What about GVHD—especially acute graft-versus-host disease versus chronic, even? Which comes first — CMV then GVHD? Or GVHD then CMV? Still, lots of you know things to learn about that.

And we know there is many studies showing higher risk for acute GVHD in T-cell–depleted grafts, as well as chronic. But what’s more interesting—what we’ve been, you know, seeing over—or try to, you know, look for, for the past 10–12 years, the indirect impact of CMV on all-cause mortality and non-relapse mortality after stem cell transplant. And there are so many studies showing — if you don’t want

to call it evidence, at least a signal — that yes, being CMV seropositive or having CMV viremia puts them at a disadvantage for survival after transplant. Most of the patients don't die from CMV but from the indirect effect of CMV. It could be a surrogate marker of immune system when you have CMV viremia—that's why it may have an impact on non-relapse and overall mortality.

So what did we accomplish over the past 20–30 years when it comes to CMV? From the 1980s, when we started doing stem cell transplants and more for solid organ transplants, we knew CMV was one of the most common infections and complications after these transplants.

So at least diagnostically, we moved from shell-vial from culture to CMV antigenemia. I remember when I started at MD Anderson in 2002, we used to do CMV antigenemia for a few years. It was a non-sensitive test, especially during the, you know, early engraftment period. If you don't have much of cells, you may not find positive CMV antigenemia—the patient may have reactivation, but we moved away from it. Hopefully, most of us now use molecular assays—PCR—looking at quantification of CMV viral load. This is very important.

But also, we added another tool for diagnostic is the CMV cell-mediated immunity. Unfortunately, we don't have time to talk much about that, but another, you know, diagnostic test that can help us determine is the patient is at risk for reactivation. Do we need to prolong prophylaxis? Do we need to treat low-level viruses? So many questions that this extra tool may help us. Stay tuned, you know, waiting for more data, but hopefully it will make it into the guidelines.

Now, what else did we accomplish? You know, I've been involved with more than 20 clinical trials for preventing CMV infection in stem cell transplant or treating CMV infection either antivirals, monoclonal antibodies, vaccines. We were not successful for years, but we learned as we go. What happened? What was going on?

But until the end of 2017, you know, we got one drug which is letermovir for primary CMV prophylaxis. You know, it was a pretty successful story. I'm going to go over a little bit of the data. But also, another success story is maribavir, which is indicated for resistant and refractory CMV infection— difficult-to-treat cases, complicated cases of CMV infection—and this was by the end of 2021.

So at least we were successful to get two drugs to the market. But it's not probably enough. We need to do more for prevention or for treatment. What about preemptive therapy as well? What else can we do for that?

But we've had some advancement over the past 20 years. Why do we want it more drugs or we need new strategies? Because the drugs we've been using for more than 20 years, from ganciclovir, cidofovir, foscarnet, or even valganciclovir—the oral prodrug of ganciclovir, a prodrug, you know—we know they work, they're effective, but they're plagued by very serious toxicity.

And when I talk about serious toxicity, I'm talking about myelosuppression from, you know, ganciclovir. And the reason you know why it's important in stem cell transplant—it's all about the graft. You know, you cannot lose the graft by myeloid suppression using drug to do that, so we don't. So our first-line therapy for CMV actually is foscarnet. You know, who cares about the kidneys? But we don't want to lose the graft — that's how we think. You know, you have to look at which is the worst.

You know, and the kidneys—and mainly foscarnet and cidofovir affect the kidneys — you see more nephrotoxicity. And we're talking about high incidence, but also very serious. You know, in the past, we used to see patients even end up on dialysis because of foscarnet use for different diseases.

The other problem with these drugs they are common—we can common mechanism of action. They all act at the DNA polymerase, so you can see cross-resistance between ganciclovir and foscarnet, or foscarnet and cidofovir, or you know, the three drugs as well.

So there's a big, urgent unmet need. That's why we've been doing all these trials to get much more safer and effective drugs to prevent or treat CMV infection after stem cell but also in solid organ transplant, they have the same issues of course with these drugs when they're used.

So, you know, when we talk about new drugs, we start, you know, with the mechanism of action of the old ones, from cidofovir and ganciclovir—ganciclovir need UL97 to be phosphorylated. CMV UL97 gets phosphorylated and then more phosphorylation at the cellular level, and act on the DNA polymerase. foscarnet acts directly on the DNA polymerase; cidofovir needs some phosphorylation before inhibiting DNA polymerase, as you see it here. So that's why you may see cross-resistance at the end when you have UL54 resistance, then, you know, some specific codons you're going to see some resistance to all the three drugs.

Now, maribavir — different mechanism of action but I'm going to caution you about one thing—it inhibits UL97, which is the, you know, inhibits morphogenesis of the virus by inhibiting egress phenomenon, encapsidation, and virions formation.

But the one issue that you need to remember with maribavir mechanism of action if it inhibits UL97, which is the enzyme needed for phosphorylation of ganciclovir, they're going to be antagonistic. So if you remember something: don't use them together in combination

—it could have an antagonistic effect.

Now, letermovir — totally different mechanism of action. It works on the terminase complex as you see it here on the right side of the slide on UL90, 56, 89, and 51, and you know, during DNA elongation, it will inhibit DNA elongation, as you see, and then virion, you know, encapsidation. So, totally different mechanism of action, and there's no cross-resistance with any of other anti-CMV drug listed here.

So what we've been doing, what kind of strategies over the years—you all remember preemptive therapy or prophylaxis, right? What I mean by preemptive therapy: you do surveillance on a weekly basis, looking for CMV viral load in the blood—in the plasma or whole blood—once a week, twice a week, sometimes in high-risk patients. If it's positive above a certain cutoff, you start therapy with anti-CMV drugs for a short course. This way you don't expose patients for a long period of time to toxic drugs. Then you stop and you monitor again. This is preemptive therapy. Prophylaxis—you start prophylaxis before any reactivation and during the high-risk period. So this is the difference between the two.

I'm not going to go over the pros and cons that you're all familiar with, but two things I need to bring up: what the difference between the two strategies that we're learning over time now, because now we have a drug for primary prophylaxis.

First, we know that with preemptive therapy, allowing the virus to reactivate after hematopoietic cell transplantation, you're putting put patients at a disadvantage for survival—increase in all-cause and non-relapse mortality—by only allowing the virus to reactivate. And this is the indirect effect—as I mentioned earlier, they don't die from CMV—very rare from CMV end-organ disease—but the indirect effect—allowing the virus, and there are many studies to show that.

Now for prophylaxis, actually the one thing that we're learning—you're putting patients on letermovir for primary prophylaxis until day 100. You stop it. If they're still at risk, they're going to reactivate after day 100. You extend the duration to day 200; you stop it at day 200. After day 200, if they're still at risk, they're going to reactivate. We're delaying immune and CMV-specific immune reconstitution by doing a great job in suppressing the virus and not having antigen exposure for T-cells to reconstitute against CMV. These are the two main things you need to remember between the two strategies.

We talked about letermovir's mechanism of action, and now we know it's approved for adult and pediatric after stem cell transplant, but also kidney transplant. But here in stem cell transplant recipients who are CMV-seropositive for primary prophylaxis as well as up to day 100. But now it's approved for extended duration in high-risk patients after day 100; they may be continued on, you know, letermovir for primary prophylaxis.

In fact, no significant side effects, I would say, either myelosuppression or kidney, you know, failure or nephrotoxicities that we can tell. You know, we've been using it for more than 8 years, with no signals really for any serious toxicities.

Now, all these indications were based on two landmark studies. The first one, the phase 3 trial, as you see here that you're all probably familiar with, led to its approval for primary prophylaxis in adults, looking at clinically significant CMV infection at week 24—like 10 weeks after stopping prophylaxis—found that around 37% on letermovir had this kind of outcome, versus only 60% more—or 60% if they were on preemptive therapy or placebo. But when we look at week 14, we had incidence in the infection—19% versus 50%.

Interestingly, now every study that we look at from around the world, looking at primary prophylaxis, you know, kind of breakthrough on letermovir, it's around 18 to 20%—same as we saw in the phase 3 trial as well.

But the icing on the cake from that phase 3 study, again, another signal, one of the exploratory endpoints which was all-cause mortality at week 24, there were a difference. If you were on prophylaxis with letermovir, you had lower all-cause mortality than being on preemptive therapy. Like many other studies showed, but at least in a prospective trial like this one, this was one of the strong signals showing impact on all-cause mortality, at least at week 24.

Now, the other landmark studies—after day 100—we saw some patients who reactivated after stopping letermovir. They were high-risk patients. They either had CMV viremia before day 100, they were on high-dose steroids, they have acute GVHD, or even chronic GVHD, they needed extended duration. We conducted the 200-days extended-duration trial and found the difference between continuing letermovir—only 3% up to day 200 reactivated—versus 19% if they were on placebo, showing that, and this was up to week 28.

And then when you stop letermovir after day 200, some who received letermovir and still at high risk, they reactivated again. But these patients did well after treatment with antiviral drugs.

Alright, let me go over a case. This is before letermovir to see, you know, what we used to see—and it was very common. Actually, we were so busy on the stem cell transplant team, you know, being consulted to really deal with these old complicated cases of CMV

infection. We used to get at least one to two consults per week with these kind of cases.

A 61-year-old male with a history of acute myelogenous leukemia underwent a matched unrelated donor stem cell transplant—donor negative, recipient positive. So in stem cell transplant, being recipient positive puts them at high risk, and having donor negative also high risk of CMV complications. And patient got conditioning with fludarabine, busulfan, melphalan, and ATG.

So day +26, the patient had a viral load of 950 IU/mL—international unit/mL. We started him on foscarnet early after transplant. There's no way they're going to get ganciclovir in our institution; we don't want to lose the graft. But he got started on foscarnet, renally adjusted. He had borderline renal dysfunction, and then the viral load became undetectable after 2 weeks. And what we did, so we stopped. At day +55, the patient had grade 3 skin GVHD and had to be started on methylprednisolone at 2 mg/kg/day.

My first polling question: What would you do at this point?

Alright—valgan for secondary prophylaxis, restart foscarnet, oral letermovir, or consult ID. I'm not sure. Okay, most of you know because you are all ID in the group. So it depends on the audience, you know what you have to answer. So good.

So I will tell you maybe there is no real right answer to that, but this patient did very well with foscarnet. Now he's at higher risk again for CMV reactivation. The problem with CMV is it's not only a one-time issue. You know, if someone has CMV viremia or activation, it's not only one time unless you do something about it—it could be multiple episodes. All the studies that we look at, you know, show on average two to three episodes or reactivations per patient if they're still at higher risk. So here, probably secondary prophylaxis would be the way to go.

And you know, letermovir now, actually part of the American Transplant Guidelines, is recommended, you know, kind of optional for secondary prophylaxis based on no indication or the data, only a few data from France and other parts of the world.

So this patient had recurrent CMV infection at 5500 IU/mL. He didn't receive prophylaxis, so it was not unexpected. So we started him on valgan at 900 PO BID. His viral load declined to 950 14 days later, but he also had decline in absolute neutrophil count. It's not unexpected. So what we do usually, we see some side effects, we try to adjust the dose, put them on once a day. Same thing sometimes with foscarnet—we reduce it, put patient at risk for resistant or refractory. Five weeks later, viral load went up 38,000 IU/mL. He was on maintenance or, you know, secondary prophylaxis, and genotypic assay was submitted. At that point, we were suspecting resistance. We switched him to foscarnet. So before, you know, you do genotypic analysis, and you switch to a drug when you suspect refractory, and he responded—950 IU/mL—but worsening of his kidney function. So this is a pretty common scenario that we used to see quite a bit.

And he had also not only kidney dysfunction—foscarnet can cause other side effects: nausea, sometimes genital ulceration, and electrolyte imbalances as well. So we switched him back to valganciclovir, adjusted to 450 oral BID, renally adjusted, and his viral load hovered over 1200 IU/mL, and this is for 2 weeks.

Genotypic analysis came back after a few days, and we found a UL97 mutation, which is the A594T. And so it is ganciclovir-predicted resistance, which was not also unexpected when a patient being on low-dose valganciclovir and being exposed to ganciclovir repeatedly.

So what would you do at this point? It is a very difficult situation—someone with creatinine of 3.2, would you, you know, start foscarnet? What about combination and IV cidofovir? Or consult ID? You know consult ID because you're the expert.

So let me show you what I think. So here, the patient was being nauseous on foscarnet, so using valganciclovir orally may not be the way to go, but it could be start sometimes—you have to if you cannot use IV ganciclovir. Now, creatinine of 3.2—putting them on foscarnet again, they may end up on dialysis. I had a few cases—a few patients end up on dialysis because you have to push through for foscarnet, especially when you have end-organ disease.

Combination—very serious toxicities. All the data that you see, every time we use combination ganciclovir with foscarnet—either low-dose ganciclovir/high-dose foscarnet or the other way around—you're going to see serious toxicities. You know, and it can happen.

IV cidofovir—I don't like this drug to treat CMV viremia or even end-organ disease. Maybe only retinitis. Our experience with it is not great, even in preemptive therapy, it doesn't work that much, you know, in my experience at least—so suboptimal and also serious toxicity. Someone with kidney dysfunction, that's not the way to go.

You should, of course, we need to get ID, but also counsel transplant ID, because, you know, they may have more experience dealing with CMV than regular or general infectious disease, because this is pretty hard, you know, what to do in this case. You know, we may use CMV T-cell infusion—we have a protocol at our institution, we use it quite a bit in the past as well. So there's no single right answer to this.

But what we did here—because of the specific mutation's low-level resistance—we used high-dose IV ganciclovir. We didn't want to go oral; we wanted to make sure the patient was getting the right dose. So we went IV, and his CMV went down to 950 IU/mL, but he had severe neutropenia and thrombocytopenia despite G-CSF support and platelet transfusion.

So it can become a kind of vicious circle here—you create all these serious toxicities, you try to deal, and the patient don't respond. And in the end, the patient going to die. And this is the all-cause mortality—they died from septic shock, from E. coli, and multiorgan failure. Because these kinds of patients, we tend to forget, when they get into trouble with CMV, they have many other complications going on with this patient—not only related to CMV as well—so this is why they have a higher risk of dying at that point.

So how do we manage refractory or resistant CMV infection in the current era as clinicians? First, how do we define refractory? If you look at the before—you know, for a long time, we were publishing on refractory and resistance, but the definitions and methods, it was all over the place. So this is what we decided—this is the Transplant-Associated Viral Infection Forum—that we need to try to at least define refractory and resistant CMV for clinical-trial use, because you want to make sure that when you develop drug for it, you're using a standardized kind of definition, but at the same time it can be used at the bedside, for us to remember when it is refractory and when to send genotype or change therapy.

So what we did actually, and we updated the definition just recently—you know, we used to have probable versus refractory. We said no, you know what, make it as refractory CMV infection. What do we mean by that? When you have increase in viral load of more than one-log increase after 2 weeks of good antiviral therapy, the right route and dose of antivirals, don't switch, don't assume refractory in the first few days. If you get a viral load today, start treatment today, and you repeat after 3 days and it went up a little bit, that's not refractory. You have to give it at least 10 to 14 days to see if it's working, because you often see a blip, especially with ganciclovir when you treat these patients. Or if you have persistence with less than one-log increase or decrease in viral load, so when you combine these two, you have, you know, refractory but at least 2 weeks of treatment with the right antiviral and dose and drug. So this is a refractory CMV infection. And CMV end-organ disease is refractory when a patient is not improving after 2 weeks or they're getting worse after 2 weeks of treatment with a good antiviral drug.

Resistance: if they have refractory, you send genotype, they have mutations—UL97 54, or even 56—then it is resistant CMV infection. Okay? But they have to have refractory first in order to suspect whether it is resistant. And then you send it to *a*—this is what we mean by resistant CMV infection.

Okay. Now, what are the risk factors for resistant or refractory CMV infection? It has to do with antiviral exposure—either prolonged antiviral exposures versus previous antiviral exposure, drug exposures, or suboptimal drug exposure, or inadequate absorption. Something to keep that in mind, especially when you have oral drug, malabsorption as well put patient at risk as sub-inhibitory concentration of the drug, where you may lead to refractory and resistance.

The type of transplant, the virus, the exposure, but also the host if they are heavily immunocompromised because of the type of transplant, the immunosuppressive therapy, put them at risk. Is it matched-unrelated donor, mismatch, haploidentical, or cord-blood—a very high level of, you know, immunosuppressions and think longer engraftment, so could be at higher risk for refractory or resistance.

But what are the protective factors? We found in one study actually that we published a few years ago, that being donor-positive, it could be a way to, you know, prevent or protective against the refractory and the resistance. But letermovir primary prophylaxis was the first one to show that if you use primary prophylaxis, you not only reduce incidence of clinically significant infection but also resistant and refractory, and so it probably makes sense.

What we do to when we suspect resistance? We send in genotypic assays, available commercially, and you look, you know, they do viral sequences from amplified from blood. It can be whole blood, plasma, or leukocytes even, or other tissues. And results are more reliable actually when you have high viral load. Although now, the sensitivity is higher when you have low viral load, at least for UL56, but for others, you know, 1,000 and above, you get much more reliable because you don't want to get false positives when you have a mixed population of resistant versus susceptible or population when you have low viral load.

But also you can have false negatives to insensitivity in detecting mutant subpopulations actually when it's less than 20 or 30% of the total. When you have these mutants less than 30%, you may have some false negatives you may not see. So you treat with the antiviral drug, and then you are predisposing to rebound, and then you start seeing more resistance.

So, genotypic assays are recommended now in the guidelines when you suspect refractory infection. You want to know if your patient has resistance or not because this may affect outcome, and then you know which drug you need to use. Refractory is much harder to treat when you have no mutation and no resistance because it's all about the host, the virus, and it's harder to treat—what to use, which drug, when they're not responding.

Now, to go over some mutations—UL97, we all know some specific mutations confer resistance to ganciclovir or valganciclovir. But what you need to remember is some specific mutations on specific codons confer resistance to maribavir as well. So the T409 and the most common H4 also 11Y. Now, two mutations that you need to remember confer resistance to both ganciclovir and maribavir, so you cannot use either one when you have C480F or F342Y, although one of these mutations may improve some—you know, have low-level ganciclovir resistance. But still, you know, you have to look at the type of mutation to understand which one is cross-resistant between each other.

UL54, the DNA polymerase—some mutations, you know, confer resistance to either foscarnet, cidofovir, or ganciclovir, or the three together as well. UL56 specific to letermovir, and you know, this confers resistance but no cross-resistance with other antiviral drugs.

We talked about maribavir mechanism of action. As you see here, it inhibits morphogenesis and viral encapsulation—egress phenomenon. And, you know, this is the landmark study led to maribavir approval for resistant/refractory CMV infection after stem cell transplant but also solid organ transplant. This trial was done for both populations where it was a randomized trial 2:1, either maribavir up to 8 weeks or investigational-assigned drug—could be ganciclovir, foscarnet, combination of either one—it depended on what the, you know, PI decided to use. And looking at CMV viremia clearance at 8 weeks, end of 8 weeks, at least on two consecutive testing for CMV viral load. And this was the primary endpoint.

It met the primary endpoint as you see it here in this slide. You all should be familiar with this study that was published 2 years ago. It's not moving—okay, here—and this is the result at week 8. You have more patients on maribavir who cleared their CMV viremia—almost 56% versus 24% on investigator-assigned therapy. And this was true at week 12, week 16, although this is when done. And the reason is because from week 8 and on, we didn't put patients on secondary prophylaxis. They were still at risk, but that was not allowed under the clinical trial; that's why. But still, it was statistically significant—the difference between the two on maribavir versus IAT, as you see it here. So this led to its approval for resistant/refractory CMV infection from age 12 and above.

After SOT and HCT. And the good news is, first, it's an oral drug. Second, it is not toxic. We didn't find any signal for serious toxicities. And this clinical trial—the only side effect that you need to remember, and probably if you start using maribavir, you can tell—you know, your patient will complain of some taste disturbance, metallic taste, you know, dysgeusia. But it did not lead to stopping the drug in less than 0.5% in the clinical trial. But it can happen in our patient population.

And of course, neutropenia was more common if patients got ganciclovir or valgan, and nephrotoxicity if they got foscarnet, as you see it here—pretty common in this clinical trial.

So how do we treat ganciclovir-resistant CMV infection? Think about high-dose ganciclovir, although side effects are pretty serious with myelosuppression. But some mutations confer only low-level of resistance, so know which are the mutations, and then you can use high-dose ganciclovir.

Now, when you use foscarnet and maribavir, you can use either one if you have ganciclovir-resistant infection. So you have to, you know, look at the benefit and the risk of nephrotoxicity of foscarnet. You may go with maribavir as the first line. For letermovir, I don't use it as monotherapy—you know, you should not—have low level of resistance. We don't know what the right dose is to treat infection, and you can elicit resistance down the road. Sometimes people use it in combination with another antiviral therapy, but for me, I don't recommend using it, at least for therapy. And cidofovir as well is suboptimal, I don't think—it causes a lot of serious side effects. I won't go that route.

Some additional treatment strategies—people talk about mTOR inhibitors as immunosuppressive drugs for GVHD—it has some antiviral effect and in vitro, and there is some data in SOT that may prevent some CMV viremia. We don't use this kind of strategy in HCT. Usually, we don't switch immunosuppressive therapy; maybe it's a little different in SOT.

IVIg—you know, our experience with it in treating resistant/refractory, you know, it's not great, you know, we don't use it. The only place where we use IVIg, and it is recommended as an optional, you know choice, is when you have end-organ disease, mainly pneumonitis, and this is because of the anti-inflammatory effect of IVIg. It may affect outcome—maybe there's a little bit of data from here and there. This is the only place. We use more IVIg or CMV-IVIg, and Dr. Humar will talk a little bit more about it in the SOT world than in the HCT world.

I used to use quite a bit of leflunomide—we published our experience a long time ago, where, you know, in addition to another antiviral when you have resistant/ refractory. We don't do it much anymore now with maribavir on the market, or artesunate, if you have, you know, access to it, you can use it.

Keep in mind about secondary prophylaxis now, especially with letermovir—it is recommended as part of the ASTCT guidelines, although not based on clinical trial or phase 3 trial, but something to think about, as patients are still at risk for CMV reactivation or even

resistant and refractory CMV infection.

Alright, and I will encourage you to look at the ECIL guideline that we published 5 months ago in May in *Lancet ID*, where we had this nice algorithm to guide people on how to approach patients after stem cell transplant when they have suspicion of refractory and CMV infection. We are recommending getting the genotypic assays in these patients, or phenotypic assay if you have access to that. If you have refractory without known resistance, optimize the dose. If your patient is on oral drug, put them on IV ganciclovir. But if they're not responding, switch to maribavir as the next option, and think about CMV T-cell infusions if you have access to that protocol.

And when you have specific mutations on different UL97, what to do with high-level resistance—you switch to maribavir but except if the patient has a CNS infection, you cannot use maribavir for high viral load. Also, we're seeing that high viral load by itself, it may lead to some failure of therapy on maribavir. I will tell you what we are recommending in the guideline later on.

UL54 also—you have some options here. I would encourage you to look at it, at this algorithm, to guide you at the bedside.

So, just published recently, the American Society of Transplant Therapy Series, we updated the CMV guidelines. We added maribavir as A-I choice for resistant/refractory. The first guideline we published in 2021 was before maribavir was approved. Now it's approved, that's why we added it to the guideline. We updated the guidelines, got A-I. maribavir and letermovir are very specific to CMV. You still have to use anti-HSV or VZV prophylaxis with acyclovir-based prophylaxis. Something to keep in mind. We added some new updated the guidelines on extended duration of letermovir, but also on secondary prophylaxis, and we defined blips. So, I encourage you to read these guidelines as well—fresh out of the oven, just recently published.

So in conclusion, resistant/refractory CMV infections are treated with high incidence of CMV disease and high all-cause mortality. It's still very difficult to treat—very complicated cases with high level of mortality. And now, at least, we have another option. It's an oral drug, and it's a safer drug than what we had in our armamentarium from foscarnet to ganciclovir, we have maribavir—something to think about. And I will tell you what the new strategy we're thinking about is, in the case later on after our talk. We're going to present a few cases.

I encourage you—come to Houston in May, beautiful weather, 14th to 17th. We have the International Immunocompromised Host Society if you want to learn about all infections, including in immunocompromised patients from solid organ, stem cell transplant, autoimmune disease, CAR-T therapy, and others—we'd love to host you in Houston in the Galleria area. Please come and join us in May. Look at the website and you'll get more details.

And I want to thank you for your attention. Follow me on X, and we're going to move on to Dr. Humar for his talk.

Dr. Humar:
So thank you very much. So I'm going to focus on the solid organ transplant side, and you'll see there is some overlap, but what I'll do is I'll highlight the differences rather than the similarities.

So CMV is the most common and important viral infection after solid organ transplant. It's a highly complex virus, and you can see that the genome here is very large, encoding about 170 functional proteins. Many of these are immunomodulatory.

And why do I mention that? It's because CMV, after solid organ transplant, has a number of indirect effects. So we know about the direct effects, which are viral syndrome—which is not something that's as well described in stem cell—but viral syndrome and then tissue invasive disease. But the indirect effects are very important too, and especially the inflammation that results in the allograft. And this can result in both acute and chronic allograft injury, which is very, very important for long-term outcomes after solid organ transplant.

Now, CMV's prevention strategies in SOT are very similar, so it's either prophylaxis or preemptive therapy are the two options.

So I'll start with a case. So it's a 58-year-old deceased donor kidney transplant. She receives induction therapy with thymoglobulin at the time of transplant, which is very common, and she's on a very standard maintenance immunosuppression regimen of tacrolimus, prednisone, and MMF. So her serology is her donor is CMV seropositive, and she is CMV seronegative—so D+/R−. So unlike stem cell transplantation, this is considered the highest risk for solid organ transplantation.

So what would you do for CMV prevention?

So—oh, interesting. Yeah, okay. So first of all, where does the 6 months come from? This is what was called the IMPACT study. This was done quite some time ago but compared 6 months versus 3 months of prophylaxis in D+/R− kidney transplant patients. And the drug that was used here was valganciclovir, and what it showed that the CMV disease rate—so, disease is symptomatic disease—was 16% with the 6 months versus 36% with the 3 months. So quite a big difference. But you do pay a price, so you get an increased incidence of leukopenia.

Now, what about preemptive therapy? Well, preemptive therapy has also been studied in solid organ transplant. And this is actually a pretty recent trial that compared preemptive therapy versus antiviral prophylaxis in liver transplant patients. So this was called the CAPSIL study, and it was D+/R− liver patients, so about 100 patients in each arm, and they looked at CMV disease as the endpoint at 1 year post-transplant.

And interestingly enough, the preemptive therapy arm did slightly better. So the disease rate was 9% in the preemptive therapy arm versus 19% in the prophylaxis arm. And why is that? Well, one of the key reasons is that in the preemptive therapy arm, when they looked at cellular responses to CMV—so both CD8 on the top graph and CD4 T-cell responses—the patients in the preemptive therapy arm tended to develop T-cell responses earlier. And the idea is, if you see a little bit of viral replication, you're able to develop a CMV cellular-specific immune response.

Now, what about in kidney transplant patients? Well, this has also been studied in kidneys, and this is a recently published study looking at prophylaxis versus preemptive therapy in both D+/R− kidneys as well as R+ kidneys who are on induction immunosuppression. And they had 70 patients in each arm.

And really interesting in this study, the primary endpoint was in CMV—the primary endpoint was biopsy-proven acute rejection. And this is getting to the indirect effects of CMV. And they did protocol biopsies at 3 months, and the rejection rate was similar in the two arms—13% in the prophylaxis arm, slightly higher in the preemptive therapy arm. But interestingly enough, the subclinical rejection—meaning when you look at inflammation, tubulitis—it was higher in the preemptive therapy arm. So prophylaxis seemed to prevented some of those indirect effects of CMV.

Now, many of you responded that you would use letermovir in this setting, and indeed, there has been, as you know, a large trial comparing letermovir to valganciclovir in kidney transplant recipients. This is our D+/R− patients, and 6 months of letermovir plus acyclovir versus 6 months of valganciclovir.

And what this study showed is that CMV disease rates were very similar in the two arms—so about 10% in the letermovir arm and 11% in the valganciclovir arm—but the leukopenia and neutropenia was much lower in the letermovir arm.

So what do the guidelines say? So I'd encourage you all to read the guidelines that were just published in June in *Transplantation*. And this is the 4th Edition of the International CMV Guidelines, and I think it's the best one we've done so far—there was about 50 of us or so involved in this. And so this is what we say about prophylaxis or preemptive therapy in D+/R− patients. So for D+/R− kidneys, we recommend that you could either use prophylaxis or preemptive therapy—you could either use valganciclovir or letermovir in that setting.

For liver patients, we recommend again the same thing: either prophylaxis or preemptive therapy with valganciclovir in this setting.

For heart and for lung recipients, we recommend that prophylaxis is better than preemptive therapy, and in lungs especially, you need very prolonged courses of prophylaxis, so 12 months in D+/R− patients.

And if you're on prophylaxis and there's intolerance to valganciclovir, you can switch to a preemptive strategy, or you can switch to letermovir in that setting.

Some considerations if you're using a preemptive strategy: use the same assay and the same sample type. So if you're using plasma, always use plasma—don't alternate between plasma and whole blood. The thresholds for preemptive therapy are really uncertain, and in the stem cell programs I've seen, they tend to use very, very low thresholds to initiate therapy. In solid organ transplant, not as much. So when we polled the group for D+/R−, most people were using between 100 to 1500 IU/mL in plasma to initiate therapy, and for R+, it was even higher, so it was in the 500-to-4000-unit range in plasma. In our own center, we use 500 in D+/R− and 1000 in R+ patients.

Also, in the real world—and this we saw at the guidelines—so it's that very few people are just using prophylaxis. So what they're doing is giving prophylaxis and then, when they stop the prophylaxis at 3 months or 6 months, or whatever, they're then doing surveillance. So this is kind of a hybrid preemptive and prophylaxis, and the surveillance is weekly for about 8 to 12 weeks after stopping prophylaxis.

Now, what about cell-mediated immunity testing? There's a whole section on the guidelines on cell-mediated immunity testing. And the idea behind it is that you take the patient's blood, you stimulate it with T-cell specific peptides—so usually it's like a peptide mix covering a number of CMV antigens—and you measure the output, which is interferon gamma typically, which interferon gamma production by either CD4, CD8, or both.

And there are a number of assays to do this. There are also a number of clinical trials now looking at this. And this was a nice randomized controlled trial in 150 R+ kidney transplant patients randomized to either immunoguided prophylaxis or just standard prophylaxis for 3 months. The idea with the immunoguided prophylaxis is they did a QuantiFERON-CMV test, very similar to the

QuantiFERON-TB test, and they did it at regular intervals starting at day 30 post-transplant, and basically stopped prophylaxis if your QuantiFERON-CMV was positive.

And what they showed that the CMV disease rate was similar in the two arms, but the duration of prophylaxis was much lower in the immunoguided arm. And hence, the toxicity from valganciclovir was much lower in the immunoguided arm.

And there's been a few studies like this, and this is the basis of a new recommendation in the guidelines. So in R+ patients—seropositive recipients—we recommend either prophylaxis or preemptive therapy, again for kidney or liver. And for heart and lung, we recommend prophylaxis.

But interestingly enough, if available, we recommend performing a CMV-CMI test in R+ kidney transplant recipients and discontinuing antiviral prophylaxis in the case of a positive test. And you can do this at monthly intervals, or you can just do it at a single time point at 1 month post-transplant.

So now let's move on to treatment. So this would be a pretty typical case of CMV: a 55-year-old woman, 4 months after kidney-pancreas transplant, D+/R+, thymoglobulin induction, on standard immunosuppression with tac, prednisone, MMF. Got 3 months of valganciclovir prophylaxis and presented with fatigue, low-grade fever, myalgia. So this would be a typical viral syndrome that you see after

transplant. So you can see her temperature is 37.9, her creatinine—you might think that's incompatible with life, but that's in Canadian units. In American units, that's about 2.0. White count is 2.1, and platelets are low, and her CMV viral load is 14,000 IU/mL.

So the first question is: Well, what treatment would you start?

Yeah, so it's—okay, 50/50 or so. So normally, we would typically start valganciclovir in this setting, but both answers are right—either valganciclovir or ganciclovir. And if you look at ganciclovir or valganciclovir, they are very potent drugs for CMV, and we see a pretty good safety profile and you see a nice drop in viral load. This trial, which was called the VICTOR study, compared IV ganciclovir versus oral valganciclovir for this exact indication and showed that the two had nearly identical clearance kinetics.

The important thing to remember is, when you're treating these patients, the viral load may actually go up in the first week. And we saw that in about 30% of patients in the VICTOR study. So just be careful about over-frequency of viral load monitoring and about interpreting small changes in viral load, especially early in therapy.

So what do the guidelines say? They say that you start either oral or IV, and where you would choose IV if you have severe disease or you have concerns about absorption. Otherwise, we would normally recommend oral therapy. You treat until negative, but you might have a center-specific threshold, because you can't always get the patients to negative if you have an ultrasensitive assay.

And then after treatment, you can either monitor them virologically, or you could consider secondary prophylaxis—especially if they're high risk for recurrence, such as D+/R− lung transplant, low lymphocyte count, or if you have the ability to check cell-mediated immunity, you could check that and decide about secondary prophylaxis.

Now let's say in this patient, you treat with ganciclovir or valganciclovir, the patient remains unwell after 2 weeks still, and the viral load has gone from 14,000 to 44,000. You send off for resistance testing. You reduce immunosuppression, which is a critical part of the treatment in a patient like this. What do you do next?

So go ahead and answer. Okay, so you know all three—A, B, or C—are all correct answers actually. Our current strategy in this patient would be normally to switch to oral maribavir in that setting, although either A or B would be reasonable alternatives as well.

So let's talk about refractory/resistant in solid organ transplantation. We heard about the definitions. What I wanted to highlight is that many organ transplant patients with refractory/resistant CMV don't actually have resistance—so at least half of them don't have resistance. And the reason they're not responding is they're over-immunosuppressed, basically. So that's why it's so important to decrease immunosuppression in these patients.

Now, we saw the mechanism of action of the currently available antiviral drugs. The key thing is that they all target the DNA polymerase, and some require phosphorylation—such as ganciclovir—whereas foscarnet binds directly to an alternate binding site, the pyrophosphate binding site on the UL54.

And we see that drug resistance mutations for ganciclovir map either to UL97—which is, you know, there's about six or seven mutations responsible for about 80% of ganciclovir resistance—and some confer low-grade resistance, some confer moderate to high-grade resistance. And then they map to UL54, or the polymerase gene, and there it depending on the site of the mutation, whether you just have ganciclovir resistance or you have resistance to foscarnet or cidofovir, or all three drugs.

So what about foscarnet and cidofovir in solid organ transplant patients? So historically, we've really used foscarnet as the primary

alternative in these patients for refractory/resistance. But if you look at the actual evidence for its use, it's quite poor in solid organ transplant patients, and it's really case series basically.

And so, for example, there's a case series of 22 patients. And the main problem in SOT—and this is more of a problem, I think, in SOT than it is in stem cell patients—is the nephrotoxicity. So especially for kidney transplant patients, they don't really tolerate prolonged courses of foscarnet.

Similarly, cidofovir seems to be very, very toxic in the solid organ transplant patients, and we really don't use it very commonly at all.

So maribavir—we heard the mechanism of action, but basically, it inhibits the UL97 protein and thereby prevents nuclear egress of the virus from the nucleus to the cytoplasm.

The SOLSTICE study that Dr. Chemaly covered also included about half of the patients were solid organ transplant patients. Importantly, the viral loads in this study were relatively low, so the median viral load was 3,377, and about 70% of patients had a viral load less than 10,000. So that's important to understand when you're looking at this study and interpreting the results. But nonetheless, as you saw, the maribavir was quite a bit better than the investigator-assigned therapy, which was typically either ganciclovir or foscarnet as the comparator in this setting.

Now, one of the key things that was looked at in the follow-up to the SOLSTICE study was the emergence of resistance, and this does seem to be an issue. So when you use maribavir, you can expect about a 25% rate of emergent resistance, and the resistance maps to UL97 but tends to map to different codons than we see for ganciclovir resistance—although there are a couple that, as Dr. Chemaly mentioned, confer cross-resistance to ganciclovir and maribavir. The three most common maribavir resistance mutations are listed right there.

When do you suspect maribavir therapy? Well, clinically, if you have a patient on maribavir and their viral load goes down, and while they're still on maribavir the viral load starts to go up, they have a very, very high rate of resistance. In this study, it was about 86% of those patients had resistance. So that's your clinical clue—if you have a patient on maribavir and the viral load starts to go up.

Now, the algorithm for treatment of refractory/resistant? So there's a very nice algorithm in the guidelines. It's quite a bit more complex than this, but I simplified it just for ease of a slide. And basically, what you do is if the viral load is low to moderate, you start the patient on maribavir. If the viral load is high—and in the guidelines, what we decided on as a threshold—and it's a rough threshold—it's 50,000 IU/mL—you initially start with foscarnet. And then what you can do is once you have some virological control, you can step down to maribavir. If you have CNS disease or retinitis, you should use foscarnet in those settings rather than maribavir. And then, once you get the resistance testing back, you can tailor your antiviral regimen based on that.

So this is some pearls from the guidelines. So if you have refractory CMV but no detectable drug resistance, you could either switch to maribavir in those settings, or you can continue with ganciclovir, adjust immunosuppression. If you have resistance, you should switch to maribavir unless the viral load is high—in which case, as I said, you start foscarnet and then you can step down to maribavir once you get some virological control.

Now, what about combination therapy? So this is a very common question that I get asked, and there really is—it's like a data-free zone, okay?—there's no data at all; it's case reports. But nonetheless, a lot of us do use combination therapy in really hard-to-manage patients. So here are some considerations. So in the past, people used to use ganciclovir plus foscarnet to try to spare the foscarnet toxicity—so don't do that. I don't think there's any evidence to support that.

Adding letermovir—I mean, it's a theoretical benefit because you're targeting two different viral enzymes. So you could add letermovir to ganciclovir, foscarnet, or maribavir. Again, there's no data to do that, but people have done it in very, very difficult-to-manage cases. Ganciclovir plus maribavir—don't do that, because the two are antagonistic. Because remember, maribavir inhibits UL97, which is needed to phosphorylate ganciclovir.

What about adding immunoglobulin? Actually, in the guidelines, we suggest that you could consider adding immunoglobulin if you have severe disease and refractory/resistant CMV disease. And so you could add either CMV immune globulin, or just regular IVIg, with many of the experts in the guidelines preferring the CMV immune globulin.

And then other agents that are currently being investigated—and like, there's an ongoing study of artesunate plus ganciclovir—but these are best done in the the form of a clinical trial.

So I think, in summary, this is a pretty exciting time to be in the CMV field. Lots of diagnostic, therapeutic, and preventive strategies are being developed. And CMV has always been called, in the SOT world, the "troll of transplantation," because it's been the Achilles' heel of transplantation. But we've made a ton of progress in defeating this troll.

This is the Guidelines Group when we convened in Montreal back last June, actually. So thank you very much.

So the first case is actually mine. So this is a refractory/resistant CMV case. Okay, so it gives you a chance to implement some of what you've heard today. So a 62-year-old, 10 months post double lung transplant, standard immunosuppression, D+R-. Okay? He's on valganciclovir prophylaxis. So he's 10 months, so he would get a year of valganciclovir prophylaxis, but he's been on and off it due to leukopenia, which is very common in these patients. And he presents with a 2-week history of fever, fatigue, malaise, shortness of breath, diarrhea, temperature's elevated. Creatinine's about 1.8 or so. AST, ALT elevated. White counts low. His viral load is 35,500 IU/ml in plasma.

And so what treatment would you start at this time? Yeah, so a mix. Again, there's no super right or wrong answers in these. I think the oral valganciclovir is probably a wrong answer in this case—and it's 0—so I think the other three are reasonable.

So we started him on IV ganciclovir, reduced his immunosuppression. However, after 2 weeks no clinical improvement, the viral load is 62,000, and a UL97 L595S mutation is found, which is one of the most common mutations conferring ganciclovir resistance. So the question is, what do you do next for this patient?

Yeah, so we would normally use foscarnet in this setting, given how high the viral load is, but maribavir is certainly an option. IV gan, for that particular mutation, it confers a relatively high level of ganciclovir resistance, and so increasing the dose of ganciclovir doesn't typically work for that particular mutation.

So the other question is, so he's a D+R- lung transplant, would you add immunoglobulin in that setting, CMV immunoglobulin or IVIg? Go ahead. 50/50. Yeah, that's about right. So yeah, the data is very weak, and in the guidelines, we say you could consider it. So it's a weak recommendation, but this is, if we're going to use it, this might be a setting that we would use it in, basically.

Dr. Humar:
So this patient started on foscarnet. He had a good response but developed worsening renal function, which is classic of what we see. So these patients do not tolerate prolonged foscarnet, but you can see the viral load goes down nicely. Thereafter, the viral load rebounds again to 10,000 IU/ml. He's clinically reasonably well at that stage. So now he's off antiviral therapy, and the viral load has gone back up to 10,000. What do you do in that setting?

Yeah, good. Yeah, so this is the kind of perfect setting to use maribavir in—viral load's relatively low, the patient does have some renal dysfunction, so, you know, maribavir would have a good likelihood of working in this case. And that's what happened. He also got some CMV immune globulin at that time point as well. And you can see he has a very nice response. The viral load goes to undetectable.

And then the question is, well, what do you do now? The viral load's undetectable, he's on maribavir, what do you do? And this is right out of the new guidelines, and it says when to use secondary prophylaxis and what to use it for. So assess the individual risk: CMV serostatus, lung transplant, recurrences, lymphocyte count, immunosuppression, and cell-mediated immunity. And this patient has all the risk factors for recurrence. He's a D+/R- lung transplant, pretty heavily immunosuppressed. He's already had one recurrence as soon as he stopped antiviral therapy.

So the options would be secondary prophylaxis with valganciclovir preemptive strategy or secondary prophylaxis with letermovir. And so the question in this audience is, well, which of these strategies would you use next? So go ahead and answer. And the answer is, yeah, switch. So yeah, so switch to secondary prophylaxis with letermovir is what we would typically do. So valganciclovir, remember, he does have that mutation, so unless for some reason he converted to wild-type, you wouldn't expect the valganciclovir prophylaxis to work. But you could also stop and monitor the patient as well—that would be a reasonable strategy. So this patient did get secondary prophylaxis with letermovir in that setting.

Dr. Chemaly:
Thank you. Thank you, Atul, for the great presentation. So this is the last case, and hopefully we have some time for questions, getting the nice questions here. So let me go over a case, also of refractory/resistant in a hematopoietic cell transplant patient. And this is a real-life experience with maribavir. We published last year the first 11 cases that we used maribavir, and this is one of the cases: a 32-year-old man with AML, status post matched unrelated donor transplant, D+/R+, and conditioning with what you see here. He had early HHV-6 viremia during the first month, and was started off for foscarnet. I don't think it was right, you know, now with the recommendation: don't treat unless you have end-organ disease, and the patient had skin GVHD requiring high-dose steroids. Three months post transplant, he developed CMV viremia at 11,200 IU/ml, and it was treated initially with foscarnet for 2 weeks, with an increased viral load to 17,800 IU/ml.

So patient had borderline kidney function with creatinine of 1.4 and ANC of 980. What is the appropriate next step for this patient after a genotype was ordered?

Okay. Switch to foscarnet or switch to maribavir. At least, you know, now in the guidelines, the American Society of Transplant and Cellular Therapy Guideline recommending if someone has worried especially we worry about toxicity from foscarnet, then to start with maribavir as a first line. So the option is usually foscarnet or maribavir, but it depends on the patient and what their underlying disease and their kidney function. And switch to IV letermovir, we will talk a little bit. I had a few questions about letermovir for treatment of CMV infection. I will talk about it later.

So CMV genotypic assay did not identify any mutation, and that's what Dr. Humar mentioned: most of the time, it's refractory without specific mutation or resistance, which makes our job a little bit more complicated or more difficult. So patient was switched to combination therapy with short-course foscarnet and maribavir. And this is the disease—patient had high viral load. What we are recommending in this guideline is an optional strategy. And also Dr. Humar mentioned it a little bit in their guideline, they're saying, start with short course of foscarnet, then continue with maribavir. For us, what we're seeing is maybe combination foscarnet and maribavir—foscarnet for a few days reduces the viral load, because that impacts viral load much quicker than ganciclovir, and then continue with maribavir. This way you can prevent serious toxicity. Maybe this is an optional strategy, not based on real data or evidence, but based on some experience with some of the cases that were difficult to treat. So that's what we did in this case, in our center.

So CMV viral decreased, you know, from 17,800 to 123 IU/ml at 4 weeks from switching therapy. So it takes some time, but now it becomes almost undetectable.

So patient was continued on maribavir for long period of time, 63 days, and CMV viral load rose again. So it went up to 120,000 IU/ml, and this is because patient had GI GVHD and possible malabsorption. Something to keep in mind: someone on oral drug when they get GI GVHD malabsorption could be here. And now we have rebound, and we have positive high viral load.

So my next question: what is the appropriate next step for this patient at this point? Alright, switch, order genotype, and switch to foscarnet, or continue maribavir? Here, I would say we're suspecting maribavir resistance, and this, based on the SOLSTICE trial and follow-up publication that patient will get rebound viral load while on maribavir if they had the resistance in more than 30% is the maribavir. So something to keep in mind, especially when you're using oral drug when you're suspecting malabsorption.

So genotypic testing detected UL97 mutation, which is the C480F, which confers resistance to both maribavir and ganciclovir at the same time. So we had to switch patient to foscarnet, and we added leflunomide. So it's been a long time we didn't use leflunomide. It has some antiviral in vitro, but we never use it alone. It may

control CMV viral load, but it may not reduce it to undetectable. But we added leflunomide, where not only that we added also CMV-specific T cell infusion based on part of a protocol that we have. And patient had no end-organ disease, and his viral load decreased to 160 IU/ml. But at the end, the patient, despite he responded, he died from GI bleed due to GI GVHD. So we could not save this.

And this is to come back to my point that I made earlier—especially when they end up with this kind of infection, refractory/resistant, multiple courses, they have many other complications going on, and toxicities going on, and they may not survive.

And this is the graph where we use the, you know, ganciclovir, then maribavir, then you see a rebound while on maribavir when they got GI GVHD, and they responded very nicely to foscarnet, you know. And in this case, patient got, you know, multiple other, you know, strategy also to control CMV.

Dr. Humar:
We have a lot of questions, so we'll just try to get through a few of them. The first question is for Roy: So the role of cell-mediated immunity, interferon gamma release assays in the management of CMV infection in stem cell transplant?

Dr. Chemaly:
Yeah, so I didn't have a chance to talk a little bit about it. I know that Atul talked a little bit about SOT. So there are many opportunities when can we use these tools at the bedside. Because this is what's important. First, we're talking about extended duration of primary prophylaxis, from 100 days to 200 days. What about testing for CMV-CMI? If it's positive, maybe we can stop prophylaxis and patient is not on steroid, and patient has good CMV cell-mediated immunity. What about if you have low-level viremia? And we see it quite a bit, you know, around 200 IU/ml, 300, even 400. Do you treat or you don't treat? We have good data we published around a few years ago where, if you have good CMV-CMI and you don't treat, patient may not progress. So many opportunities, I would say. But we need to have some more intervention trial in HCT that didn't do a better job in SOT to define than in HCT.

Dr. Humar:
The next question is: Any suggestion for patients with dysgeusia caused by maribavir?

So what I do is, first of all, it's very important, you have to tell your patients before they start maribavir to expect that, and that they have

to kind of carry on and they absolutely cannot miss a pill. And then, if they have it and it's a problem, I tell them to try things like, you know, mints or lemon juice, or you know, chili—some people like chili peppers. There's all sorts of different things that people have tried to try to decrease that. Some people also have concurrent nausea and stuff, and you can use antiemetics in that setting. But it's absolutely important they don't miss any doses.

And then the next question is: What's the treatment for ganciclovir-resistant, maribavir-resistant CMV viremia?

Dr. Chemaly:
Yeah, we don't have much of options.

Dr. Humar:
Yeah. So, I mean, sometimes those still remain sensitive to foscarnet, so that would be the treatment of choice in that setting. If it's resistant to foscarnet as well, then you're really running out of options, and you need to look at kind of alternative therapies, like maybe a combination with letermovir and CMV immune globulin. Or if you have access to cellular therapies, that might be a good option at that point as well.

Dr. Chemaly:
Yeah. Or if you have access to artesunate, have some antiviral, anti-CMV in vitro. There's a trial ongoing, I don't think it's in the US, on leflunomide, but it's all as an alternative.

Dr. Humar:
Our next question is for Roy from a pediatric infectious disease specialist from Colombia: Any experience using letermovir for the treatment of refractory/resistant CMV infection in stem cell patients? We don't have maribavir available in our country.

Dr. Chemaly:
Yeah, unfortunately, you know, I'm discouraging use of letermovir as a monotherapy in this kind of cases, or even for preemptive therapy. We don't know the dose, and you can create more resistance. But I know there is a few centers who they use it in combination with maribavir, or maybe ganciclovir. So if you're going to use letermovir, it has to be in combination as combination therapy. But it's not the best option to treat resistant/refractory CMV.

Dr. Humar:
Next question is: Previous definition of refractory CMV was greater than one-log increase compared to peak viral load during the first week of treatment. Is this no longer the case?

So now you need to treat at least 2 weeks before you think about defining refractory or resistant CMV. And the reason is, in the first week, sometimes the viral load actually goes up anyways, because what you get is that, as in the tissue where most of the replication is actually occurring in the tissue rather than in the blood compartment, you get release of dead viral fragments, basically, and so the viral load can go up.

Dr. Chemaly:
Right. And you compare the log to the peak viral load in the first week. That's also what we meant, and it's still in the definitions as well. You know, when you look at 2 weeks of treatment, you compare to the peak viral in the first week to determine if it's more than one-log increase or less than one-log increase.

Dr. Humar:
Next question is for you, Roy: So in the post-allogeneic transplant setting, based on your experience, when patients present with very high CMV viral loads without resistance or refractory, do you consider high-dose ganciclovir, or would you use foscarnet, or dual therapy?

Dr. Chemaly:
So if you have very high viral load, and you're not suspecting refractory yet, it's an initial presentation. You know, I would say foscarnet; it's a much quicker mechanism of action directly on the DNA polymerase, where you see a quicker drop in viral load than ganciclovir. Ganciclovir can take up to 2 weeks maybe to start seeing. I may use foscarnet, especially if someone is early after stem cell transplant. I won't go with combination therapy if you have high viral load unless you use a monotherapy and it's not working—different story. We don't want to expose patients to serious side effects from the get-go where we don't know—they may respond quickly, even with high viral load—initial high viral load.

Dr. Humar:
Yeah. And for solid organ transplant patients, in that setting, we would use IV ganciclovir, not oral valganciclovir. We wouldn't use foscarnet. We would use IV ganciclovir at a normal dose, and we would try to decrease immunosuppression as well if they present with

a very high viral load.

For refractory/resistant CMV, is there an IV formulation of maribavir?

So there is no IV formulation; it's oral only.

What does this say? Oral can it be used as rectal suppository? So, no.

Dr. Chemaly:
Ooh, no, I don't think it's available yet. So I think for this pediatric, maybe talking about pediatric patients.

Dr. Humar:
For Dr. Chemaly: What do you think about increasing the maribavir dose in patients with gastrointestinal GVHD grade 2-4?

Dr. Chemaly:
I'm not sure. I think the 400 twice a day is the optimal dose, and they have done studies, safety studies, up to 1200 twice a day if I remember well, and, you know, 800 twice a day, and they found the same effect, you know, on viral load. So, you know, for GI absorption, there's no data. I'm not aware of any pharmacokinetic data increasing if you see better absorption in GI GVHD. You know, I mean, I don't know if I would go this route or not. I would stick with the recommended dosage for that.

Dr. Humar:
Yeah, we don't know the best dose of maribavir still, and we know that people do tolerate much higher doses. But the phase 3 had the 400 BID. So I think most of us are using the 400 BID until we get data suggesting otherwise. And we don't have therapeutic drug monitoring for maribavir, yeah.

What do you do with patients who respond to maribavir with greater than one-log reduction, but continue with intermittent viral load detection at low levels, like blips?

Dr. Chemaly:
Yeah. Do you see quite often this in SOT?

Dr. Humar:
When I have hovering above low-level viral load, yeah, we see that. We see that very often, actually. And when patients switch from maribavir, we do see that. And what it tends to be is it's a harbinger of eventually they're going to breakthrough maribavir. So I think the best thing with maribavir is to get them below a center-specific threshold. And, you know, at our center, we use 200 IU/ml as that threshold, and then to stop the maribavir and put them on secondary prophylaxis with letermovir, typically.

Dr. Chemaly:
Yeah, I think this is the best approach. As soon as we have very low viral load, we switch to letermovir, instead of keeping maribavir, because they may get breakthrough.

Dr. Humar:
So after genotypic resistance for maribavir, and after foscarnet use and intolerance, what treatment options are available with rebound viral load?

I think this is similar to that previous question. You're kind of running out of options at that point. So, yeah.

Role of cell-mediated immune response, interferon gamma release assay in the management? No, I think we did that one. Yeah. Okay, yeah. So I think we were out of time, and we covered most of the questions.

Dr. Chemaly:
Yeah. Thank you all for coming this morning, and thank you.

Announcer:
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