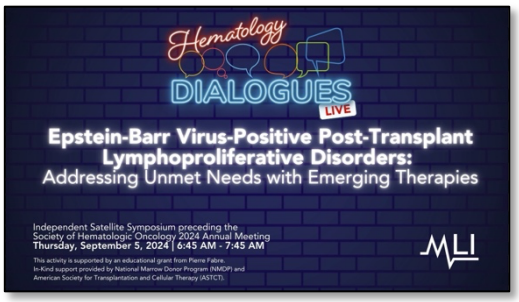
Epstein-Barr Virus-Positive Post-Transplant Lymphoproliferative Disorders: Addressing Unmet Needs with Emerging Therapies



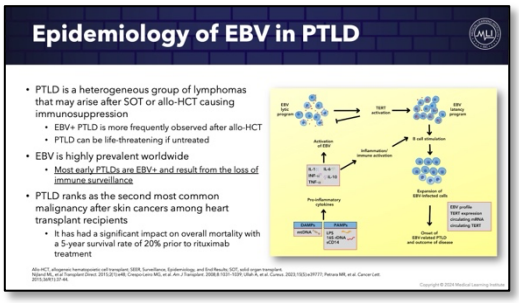
Kris M. Mahadeo, MD, MPH: Good morning. On behalf of MLI, thank you for attending the symposium, *Epstein-Barr Virus-Positive Post-Transplant Lymphoproliferative Disorders: Addressing Unmet Needs with Emerging Therapies*. This activity is supported by an educational grant from Pierre Fabre, with in-kind support from the National Marrow Donor Program (NMDP) and the American Society for Transplant and Cell Therapy (ASTCT). I'm Dr. Kris Mahadeo. I'm a professor of pediatrics at Duke University and the Division Chief for Pediatric Transplant and Cellular Therapy. With me today is Dr. Timothy Voorhees, an assistant professor in the Division of Hematology at The Ohio State University and a member of the Translational Therapeutics Program at OSU CCC. Dr. Voorhees, please tell us a little bit about yourself.

Timothy Voorhees, MD, MSCR: It's great to be with you all today. Thank you for coming. I'm at Ohio State University. I'm an assistant professor. I do have a specific interest in EBV-driven lymphomas and PTLD. I've been fortunate to be able to lead two investigator-initiated trials at Ohio State focused in treating patients with PTLD after solid organ transplant.

Dr. Mahadeo: To his left is Sarah Featherston. Sarah Featherston is a transplant nurse coordinator at MD Anderson Cancer Center. Sarah, please tell us a little bit about yourself.

Sarah Featherston, RN, CPN, BMTCN: Hi. Thank you for having me. I'm a transplant coordinator at MD Anderson. I worked with Dr. Mahadeo for a few years on the ALLELE trial, so I'm happy to be here to talk about EBV+ PTLD.

Dr. Mahadeo: Today, the three of us will engage in dialogue format by having a candid conversational approach as we explore the epidemiology and burden of EBV+ PTLD, current and emerging prognostic scoring systems for EBV+ PTLD in order to inform treatment decisions and explore the latest clinical evidence of emerging treatments based on safety, efficacy, mechanism of action, treatment, and disease-specific factors to determine optimal treatment strategies. Thank you again for joining us today. We'll get started.



Epidemiology of EBV in PTLD

Dr. Voorhees: PTLD is a heterogeneous group of lymphomas that arise after a solid organ transplant or allogeneic stem cell transplant in the setting of immunosuppression. EBV+ PTLDs are more frequently observed after allogeneic stem cell transplant. PTLD, of course, can be a very life-threatening disease in patients regardless of the transplant type.

EBV is a highly prevalent virus worldwide. Most estimates estimate that over 90% of the population worldwide have been exposed to EBV by early adulthood. We know that most early EBV or PTLDs are EBV+ and result from decreased immune surveillance of the virus lying dormant within the B-cell population. PTLDs rank as the most common malignancy after skin cancers in heart transplant

recipients, and that can be really common across a number of transplant subtypes. It has a significant impact on overall mortality.

Before adding rituximab into the treatment algorithms, the five-year overall survival rate was only 20% in heart transplant recipients. It has improved over time, but we still see a significant amount of morbidity and mortality related to this disease.

PTLDs do exist on a spectrum from early nondestructive lesions to polymorphic and monomorphic disease, with monomorphic PTLDs being the majority of what we see, and most consistent with diffuse large B-cell-like lymphoma characteristics by histology.

EBV accounts for nearly all cases of PTLD after allogeneic stem cell transplant, but closer to about half of cases following solid organ transplant. Despite seeing more cases of EBV+ PTLD, EBV+ PTLD is still quite an uncommon condition. It occurs in only 1 to 2% of patients after allogeneic stem cell transplant and can be seen in up to about 10% of the novel malignancies after solid organ transplant. Just for a little bit of a scope and how this has grown over time and the number of cases that we see worldwide.

In 2021, there were over 140,000 new solid organ transplant recipients globally, and most estimates expected incidents of PTLD somewhere between 2 and 20%, depending on the organ type and immunosuppression characteristics. There is a pretty significant population worldwide of PTLD after solid organ transplant. In contrast, in 2022, there were about 8,500 allogeneic stem cell transplants in the US, and this led to about 150 new cases of PTLD during that time period.

Ms. Featherston: Just moving on to discussion questions, I'm going to throw these over to these guys. First question would be, what factors do you believe contribute to the rising incidence of EBV+ PTLD in post-transplant patients?

Dr. Mahadeo: I think there's an increasing number of solid organ transplants that are occurring. As this also improves for these patients, they're living longer, I think you're going to see an increased incidence, likely just as a result of the fact that we're doing more of these transplants and that survival time. Beyond that, I think there are changes in how we approach allo-transplants, so HCT, whether that be changes in immunosuppression or preparative regimens that can influence.

Then the prevalence or incidence of other viral infections that could be triggering the reactivation of EBV. I think we've heard over and over in COVID, and I know there are people that have thought about that, whether the S5 protein can actually increase that. A lot of epidemiologic factors, there are risk factors from other viruses, but really also just what are we doing in transplant as well.

Dr. Voorhees: Yes, I would agree with that. I think that most transplant centers, more from the solid organ transplant perspective, have become more aggressive about transplanting organs, potentially with some mismatches, using better immunosuppression therapies than in the past. We are seeing more patients go through solid organ transplant. I think that we've also seen more of an acceptance to move a patient with, say, an EBV-seropositive donor and EBV to seronegative recipient, go forward with the understanding the higher risk of EBV complications and potentially EBV+ PTLD developing. I

think being more aggressive about transplanting patients and then increasing immunosuppression used after transplants, in some cases, are leading to an increasing incidence.

Dr. Mahadeo: I think actually, just as you mentioned that, in the allo-HCT setting, it's similar, right? Changes in post-Cy using haplo-related donors, those have increased. The indications for transplant, the eligibility for the HCT setting for non-malignant diseases, as those change as well, you would expect that there are more patients, different populations, that you could see the incidence change as well.

Ms. Featherston: Like Dr. Voorhees said, the PTLDs are predominantly a B-cell disorder, like diffuse large B-cell lymphoma being the most common. It's often extra nodal with variable clinical presentations determined by the pathologic subtype. The risk factors can be EBV serology mismatch, most specifically with the recipient being EBV- and the donor being EBV+. The type of transplant, which the risk is highest for patients who have multi-organ transplants, as well as bowel, heart, and lung transplants, and then age, and then, of course, immunosuppression.

Dr. Mahadeo: What's the disease burden for a PTLD? Dr. Voorhees has mentioned in PTLD and allo-transplant recipients, it develops earlier than in patients with solid organ transplant, and they tend to have a more clinically aggressive course and just overall results in poor survival. In both the solid organ transplant and the allo-HCT setting, the incidence is low. It's 250 per 100,000 transplants, but it can lead to significantly high rates of mortality. I think you can see the slide and the five-year survival rates for liver and kidney transplants, 64 to 70%. Heart and lung recipients, about half.

PTLD develops within two to four months, most commonly after an allo-HCT, again, earlier in the allo-HCT setting, with most cases appearing within the first year after the transplant coinciding with the immune system recovery.

Dr. Voorhees: Speaking just a little bit more to the incidence of PTLD. The incidence of EBV+ PTLD has increased over the last 20 years. This is likely due to a number of factors, including the number of organ transplants that are being performed, the amount of immunosuppression that we're using for some of these transplants. The transplant registries really have shown an increase in the incidence of PTLD over the last couple of decades.

The UNOS database looking at adult transplant centers in the early 2000s were able to report on some incidence rates of PTLD with the highest incidence being seen in lung transplant recipients, followed by liver and heart recipients, and the lowest risk for PTLD occurring in kidney transplant recipients.

Ms. Featherston: How do you think advancements in diagnostic techniques have impacted the reported incidence?

Dr. Voorhees: I think that over the last decade or two, there's been a lot of advancement in checking for EBV+ disease, both from EBER-ISH testing on samples routinely, more availability for EBV PCRs from the peripheral blood. I think there's just been a general further recognition of this issue that patients can have after transplant and that has led to increased incidence or adding to the increased incidence.

In terms of diagnosis of PTLD, due to the heterogeneity of the disease and often nonspecific clinical findings, diagnosing PTLD can be a challenge.

It's important to really consider a lot of the clinical characteristics of these patients when trying to make a diagnosis. You have to consider rejection of the allograft as a possible source of these symptoms, potential opportunistic infections, as well as other common infectious etiologies. Obviously, biopsy and imaging studies are important and necessary to make the diagnosis. Oftentimes, some of our earliest cues or clues that we could be dealing with a newly developed PTLD would be an elevation of the EBV viral load detected in the peripheral blood.

Ms. Featherston: What is the role of prophylactic antiviral treatments in reducing the incidence of EBV+ PTLD?

Dr. Mahadeo: I think we'll talk about this a little later as we go through the discussion. There are guidelines already that don't recommend that. I think I agree. I don't think that they've had much of an impact in terms of reducing the incidence.

Dr. Voorhees: I agree. I think there have been some recent meta-analyses looking at multiple studies for prophylactic antiviral treatment and ability to either prevent EBV reactivation or EBV+ PTLD, and those have mostly been neo-negative studies.

Ms. Featherston: What strategies do you think could be implemented to better manage and potentially reduce the incidence?

Dr. Voorhees: I think this is a tough question. I think the earlier recognition is really important, trying to detect or at least check for EBV+ disease or check for EBV-PCRs earlier in the course of trying to understand whether the patient could potentially be developing PTLD. There was an interesting study at ASH last year, it was more retrospective, but they looked at whether or not patients received rituximab either as an immune-suppressing therapy with their transplant or shortly thereafter before developing PTLD. Those who received early rituximab actually had a lower incidence of developing EBV+ PTLD, which I thought was an interesting study.

There are some issues with that data, but I think earlier detection and potentially earlier intervention certainly could impact the incidence or the risk of developing EBV+ PTLD.

Dr. Mahadeo: I think, again, we'll talk a little bit about viral load monitoring, but I think, again, as you standardize that to some extent, we'd be able to understand in the future how that impacts your incidence. I think standardizing both in the solid organ transplant setting and the HCT setting that sort of surveillance, maybe capturing what the interventions are in the small population, will potentially help us understand that a little better.

Then, again, I think also just as you make changes to immunosuppressive protocols, your rates of GVHD in the allo-HCT setting, how much immunosuppression are patients getting before they go to transplant, all of these things, I think as we understand more, balancing the risk of PTLD versus all of the other complications that you may be facing potentially will help us reduce the incidence.

Dr. Voorhees: The WHO classifies PTLD into four main categories. Early lesions, which are often EBV-associated, almost universally EBV-associated. Polymorphic PTLD, which, again, over 90% of the cases are EBV-associated. Monomorphic PTLD, which is the majority of PTLD that we do see and can be EBV or EBV-negative disease, as well as classical Hodgkin lymphoma. Treatment aim is obviously to cure the PTLD but maintain the transplanted organ function and obviously minimize toxicities to the patient.

Prognosis and treatment selection, there are many factors to consider as you try to think about the best treatment for these patients, but you need to consider disease-specific factors such as what kind of transplant did the patient receive, a solid organ transplant, allogeneic stem cell transplant, potentially a heart transplant or another organ that may be impacted by your treatment, the underlying pathophysiology of the disease itself and how aggressive it may be appearing. Time from transplant can have some role. Obviously, the earlier lesions we tend to think are more EBV+ oftentimes more responsive to reduction of immunosuppression and rituximab-based approaches.

Later diseases are more consistent with your true diffuse large B cell lymphoma and often EBV-negative. Then there are patient-specific factors such as their age, their EBV serostatus at transplant, and really one of the most important factors for prognosis is how they respond to reduced immunosuppression and immunotherapy-based therapy like rituximab-based therapy.

In terms of the prognostic factors for solid organ transplant recipients, we still basically use the IPI or the revised IPI for solid organ transplant recipients. Obviously age greater than 60, adverse age greater than or equal to 3, ECOG performance status greater than or equal to 2, elevated lactate dehydrogenase, and greater than 1 extranodal site of involvement are all risk factors. Obviously with increasing IPI score, decreasing survival, unfortunately.

We have not gotten to a point where we're able to incorporate other important factors such as the type of transplant the patient received and how they've responded to reduction of immunosuppression, whether or not they respond to rituximab therapy, which all are indicative of poor survival on these patients.

Ms. Featherston: Moving on to some more discussion questions. What factors do you consider most critical in estimating the survival risk for patients with EBV+ PTLD?

Dr. Mahadeo: Again, the ability to tolerate a reduction in immunosuppression I think is important, and your response to rituximab. In the allo-HCT setting, I think whether or not there's the presence of graft-versus-host disease is also going to be important in terms of survival risk and just your overall comorbidity status in terms of being able to tolerate any therapies that you might need.

Dr. Voorhees: I agree. In addition to that, I think the WHO classification of the PTLD is very important. Obviously, early lesions do extremely well, polymorphic disease responds extremely well to reduced immunosuppression and rituximab-based therapy, and then, obviously, monomorphic disease is the group of majority of the patients but the group that I think we deal with more of the issues with survival long-term. Really knowing exactly what WHO classification you're dealing with is important.

Then I would say, I would echo what Dr. Mahadeo mentioned about the response to rituximab or reduced immunosuppression or rituximab-based therapy. There's definitely data in the solid organ transplant setting. Those patients that do respond to rituximab induction alone have excellent long-term survival, whereas those who do have to go on to chemotherapy have an inferior survival.

Dr. Mahadeo: In terms of prognostic factors for allo-HCT recipients, the most common risk factors for PTLD in this population is going to be prior transplant. If this is your second HCT, your EBV viremia loads but at around the time that you're detecting this, T-cell depletion, whether that's ex vivo or in vivo, histocompatibility, so the degree of mismatch between donor and recipient, and then the serology mismatch as well, and then use of cord blood have been the most common risk factors identified.

Now in terms of inferior responses to first-line rituximab therapy, the risk factors for that would be an older age, extranodal disease. We've talked about GVHD before, so again acute GVHD, and in tandem with that is the inability to tolerate a reduction in immunosuppression. Then factors associated with poor response to CTLs or EBV-specific CTLs after prior rituximab. Some of those factors may include prior receipt of multi-agent chemotherapy, again extranodal disease, and more than three sites of disease.

Ms. Featherston: How does the EBV viral load at diagnosis influence the prognosis of patients with the EBV+ PTLD?

Dr. Mahadeo: Tim, I don't know how you feel about it. I think that the viral load itself, I don't know that it's prognostic, I think.

Dr. Voorhees: No, I agree. I don't think there's any data that supports any particular cutoff for EBV viral load indicating a certain prognosis in patients, at least in the solid organ transplant setting.

The American Society of Transplantation Infectious Disease Group also has guidelines for managing EBV viremia as well as EBV+ PTLDs. The issues with these practice guidelines are that they were last updated in 2019. They do support the preemptive strategies of targeting EBV+ PTLD, especially in patients that are EBV seronegative recipients with a donor that is EBV seropositive. They do recommend routine peripheral blood EBV measurement and testing and coupling this with reduced immunosuppression when patients do develop EBV viremia and/or an EBV+ PTLD.

Their treatment recommendations mirror the NCCN guidelines that we'll talk about here shortly, but basically recommend a sequential tailored approach with a CD20 targeting therapy with rituximab and then moving on to cytotoxic therapy if patients do not have an appropriate treatment response.

Dr. Mahadeo: So, lymphoid proliferations in PTLD, they can be attributable to PTLD, but they can be also attributable to other causes. Specific infections, nonspecific inflammation, or organ rejection. For the diagnosis, the presence of a few EBV+ cells doesn't confirm that diagnosis. Scattered EBV cells can occur in lymphoid proliferations, even in immunocompetent individuals. Really important that you confirm EBV-PTLD cases that they will typically show a latency pattern. Then the subclassification is determined after the confirmation of diagnosis of PTLD. You always want to have an excisional biopsy to confirm that diagnosis and for your subclassification.

If there's recurrence of disease, it's really important to re-biopsy, just making sure that you don't have a more aggressive PTLD that's occurring or some other second primary tumor, such as EBV, sort of smooth muscle tumors, that can also be present.

Ms. Featherston: What role does the presence of comorbidities play in the survival risk assessment?

Dr. Voorhees: I think it's pretty important, actually. There are multiple studies in the solid organ transplant setting where just ECOG performance status alone is predictive of survival. I think patients who have comorbidities or are more symptomatic from their disease are really the patients I'm worried about. I think it's more difficult to get them through. One, maybe the disease is more aggressive and causing more symptoms for these patients. Then two, I think it's more difficult to get them through treatment. There's a significant mortality rate with chemotherapy-based therapies in PTLD. I think that that plays a big role in patients who have multiple comorbidities.

Dr. Mahadeo: Sarah, I think as we saw patients together, I think that potentially with PTLD, in terms of the comorbid risk, even being willing to have more therapy.

Ms. Featherston: Correct, yes.

Dr. Mahadeo: That's an interesting perspective.

Ms. Featherston: I think, Dr. Voorhees, you talked about this earlier, but how important are the histopathological features in determining the survival risk for these patients?

Dr. Voorhees: I guess I answer that in question one. No, I think it's critically important, like I mentioned just shortly before. Like Dr. Mahadeo was mentioning, you really need more than just some EBV+ cells and some atypical cells in a lymph node on a core biopsy. You really want to make sure you have a clear architectural picture of what type of disease you're dealing with.

Ms. Featherston: In your experience, what impact does the time of onset of PTLD after transplant have on survival risk?

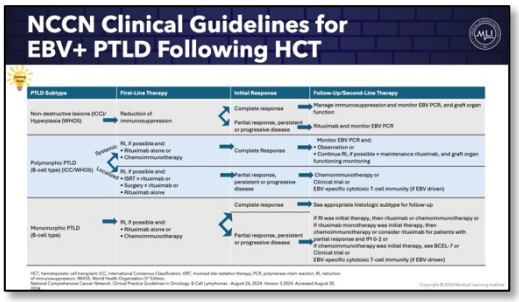
Dr. Mahadeo: I think at least in the HCT setting, if you're before 100 days, I think that's a pretty important survival risk factor in terms of how aggressive your disease is likely going to be. Again, earlier onset, but I think in particular, in that first 100-day period. Again, if you think about it, it's probably harder to reduce immunosuppression during this period in particular. It's still sort of that acute toxicity period after an allotransplant, but there's also good multi-centered data to support that less-than-100-day period as well.

Dr. Voorhees: I think in the solid organ transplant setting, there's data on early versus late PTLDs. It depends on what time point you want to select as the early versus late. In general, in solid organ transplant recipients, I think the earlier PTLDs do better. Part of that is because you probably see more early lesions and polymorphic disease, EBV-driven PTLD, which may have better responses than your traditional if you search B-cell lymphoma, occurring five years after a solid organ transplant.

I think just a little bit of a different group of patients depending on when the PTLD does occur after a solid organ transplant.

All right, so to just touch on some of the gaps in treatment for EBV+ disease. Currently, there are no FDA-approved therapies for EBV+ PTLD, and this differs a lot from all other non-Hodgkin lymphoma therapies that we have. The treatment is different and should be different than how we approach other non-Hodgkin lymphomas.

These patients are on lifelong immunosuppression after allogeneic stem cell transplant and solid organ transplant. This comes with increased risks for infections and other graft reduction as we try to reduce immunosuppression. It's also important that we continuously are monitoring for the risk of GVHD and graft loss as we treat these patients.



NCCN Clinical Guidelines for EBV+ PTLD Following HCT

The NCCN does have guidelines for treating PTLD in general and EBV+ PTLD. At the top here, you can see the non-destructive lesions or these early lesions. First-line therapy is really reduction of immunosuppression if you can do this safely. Patients who achieve a complete remission can continue on with the reduced immunosuppression and monitoring of the EBV PCRs from the peripheral blood. Patients who have a partial response can go on to rituximab-based therapy with continued reduction of immunosuppression and monitoring of EBV PCRs.

Polymorphic disease, oftentimes, this is systemic disease. Again, reduction of immunosuppression and if possible, rituximab monotherapy alone is extremely successful. Most of these patients will achieve a complete remission and then can go on to observation with either continued reduction of immunosuppression and EBV monitoring. I would say, a few patients really need to go on to chemotherapy for polymorphic disease.

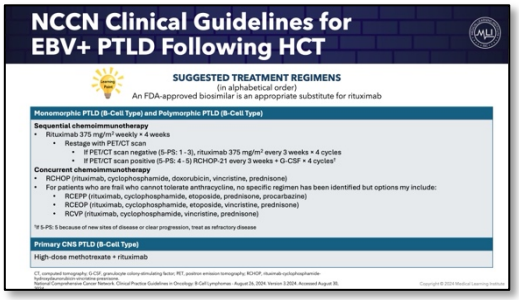
Then if you do have localized polymorphic PTLD, you'd have the option of incorporating system or focal radiation therapy or even surgery, potentially, if a lesion is appropriate to be managed this way in combination with rituximab or with just rituximab alone. Following the same treatment course there.

If patients do have insufficient response to progressive disease and are EBV+, they are potentially eligible to go on to chemotherapy at that point and then potentially even EBV-specific cytotoxic T-cell therapies.

Monomorphic PTLDs, which are the majority of the patients that we deal with, again, reduction of immunosuppression is critical for managing these patients. Rituximab alone or chemotherapy can be approached as the frontline therapy. My approach is to try to use rituximab monotherapy if we safely can do that, depending on the disease characteristics for the patient. If patients achieve a complete remission, they can go on to further maintenance for rituximab therapy for a couple more treatments.

Those who achieve only a partial response or persistent progressive disease oftentimes will go on to our traditional chemotherapies. If, unfortunately, patients are either not eligible for those

chemotherapies or do not respond, EBV-specific T-cell therapies are potential treatments for patients at that time.



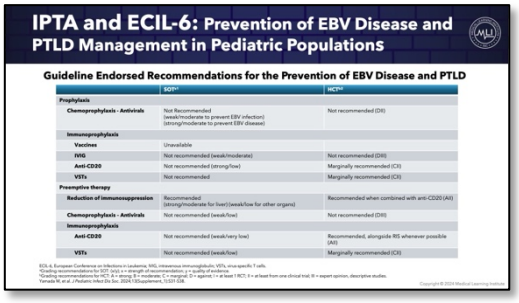
NCCN Clinical Guidelines for EBV+ PTLD Following HCT

This is just a little bit of a summary of the treatment regimens for monomorphic PTLD and polymorphic PTLD, specifically the B-cell origin types, which are the most common types that we deal with. Our options are either to use sequential chemoimmunotherapy or concurrent chemoimmunotherapy. Sequential is the approach that I typically try to use with rituximab weekly for four doses. You then restage patients with a PET scan a week or two after completing those four weekly doses. If patients are on a dual 1-3 complete response, you can move on to rituximab maintenance, what I would call, every three weeks for four additional cycles. If patients have a doable four or five response or have persistent disease, these patients typically need to move on to traditional R-CHOP chemotherapy every three weeks with growth factor support for four cycles.

This is the sequential approach, and then, of course, you can consider using concurrent chemoimmunotherapy from the frontline with either R-CHOP or for patients who are unable to tolerate an anthracycline-based therapy. Specifically, we often have to consider this specifically in the heart transplant recipient population of whether or not to use R-CHOP or to use alternative regimens that avoid the anthracycline therapy.

For primary CNS PTLD, still the backbone of therapy is high-dose methotrexate and rituximab. The primary CNS PTLDs are more rare, but we are seeing them not too infrequently. I think you can imagine with a transplant, a transplanted kidney, high-dose methotrexate is not exactly the best treatment approach that you'd want to have a patient going through. We certainly have room to improve for primary CNS PTLD.

Ms. Featherston: Factors that should be considered for this population would be things like severity of the underlying condition that necessitated the transplant, complexities of the transplant process itself, and potential risks to the transplanted organ. Then a subset of patients with EBV+ PTLD might not be suitable for chemotherapy. Recommendations to include avoiding chemotherapy for patients with characteristics like impaired organ or bone marrow function, a high ECOG score, patients with a history of stem cell transplant, and those not responding to chemotherapy.

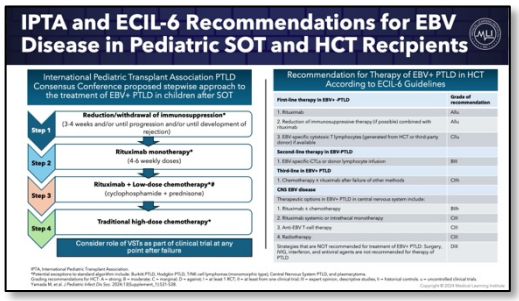


IPTA and ECIL-6: Prevention of EBV Disease and PTLD Management in Pediatric Populations

Dr. Mahadeo: There have been guidelines in the pediatric setting for prevention of EBV-PTLD. In the solid organ transplant setting, the International Pediatric Transplant Association has made recommendations. In the HCT setting, the European Council of Infections and Leukemia have also made recommendations. I think we talked a little earlier about viral load monitoring. At least on the IPTA end, the recommendations are for monitoring if you are recipient negative serology but donor positive, for essentially any pediatric patient that is recipient

negative serology. In particular, if you're less than a year old, even if you are recipient-positive, to interpret that as passive antibody from the mother. Assume there that you're negative and continue surveillance. Then any intestinal risk transplant recipient. Then on the ECIL end the viral load monitoring management is thinking through any high-risk transplant that we went through before, like your cord blood transplants and second transplant, things like that.

The guidelines that have been endorsed are really based on very limited evidence. Again, if you think of prophylaxis, and this was one of the questions that we discussed earlier, you can see that it's not recommended by either group, in terms of chemoprophylaxis and for antivirals. Then on the immunoprophylaxis end, IVIG sometimes is used, but it's not recommended by either guideline. Rituximab, marginally recommended in the HCT setting. If VSTs are available, they're marginally recommended by ECIL in the HCT setting as well. In terms of preemptive therapy, so you have viremia detected, reduction of immunosuppression with rituximab is recommended in the HCT setting, as well as VSTs, again, if they're available. This is what we have in this rare disease, based on the evidence that's available.



IPTA and ECIL-6 Recommendations for EVB Disease in Pediatric SOT and HCT Recipients

Then I think going along with that, on the solid organ versus HCT setting, I think you can see the slide. On the HCT side, you can see that the first line for PTLD is rituximab.

Best if in combination with reduction immunosuppression. Again, if EBV-CTLs are available, that's sort of your next recommendation. Really, using a more cautious approach to chemotherapy in that HCT setting. That's in contrast to the pediatric, the solid organ setting, where, again, you will attempt a reduction of immunosuppression, withdrawal, even, if you can. Then more of a sequential thought process of rituximab monotherapy, or plus-minus low-dose chemotherapy.

Just again, thinking of overall survival for these patients, success rates vary, but up to 50% of patients with EBV-PTLD are refractory to first-line rituximab therapy. If you think about what some of the factors are that contribute to a poor response, again, acute GVHD requiring immunosuppressive medication, so you need additional immunosuppression, involvement of extranodal sites, the intolerance to reduce immunosuppression, and bone marrow grafts. I think that just coincides in some ways with your immunoconstitution.

But the three-year overall survival for allo-HCT recipients with PTLD treated with rituximab-containing therapies can range from 20% to 48%, with patients having multiple risk factors experiencing the lowest overall survival rates. Overall, there's a pressing clinical need for effective alternative treatments for patients after allotransplant when initial therapies fail, because there is just no standard therapy that is available after this.

The current guidelines for managing EBV-PTLD that's refractory to rituximab are based on limited evidence, like I said. The outcomes following failure of rituximab with or without chemotherapy are generally poor, with a median overall survival of 33 days. Chemotherapy is typically ineffective and associated with a high treatment mortality rate, can be as high as 33%, further constraining the

treatment options following rituximab failure. If you remember the ECIL guidelines not recommending that upfront chemotherapy, and then now you're in the relapse refractory setting, it's a pretty tough situation to be in if you're a non-responder.

Ms. Featherston: Okay, so a few more discussion questions. What are the most promising new treatment options currently under investigation for EBV+ PTLD?

Dr. Mahadeo: I was an investigator on the ALLELE Trial, so I'm pretty excited about those results. I think beyond that-- and I think Tim can probably speak a little more, looking at what the next immunotherapies look like, whether that be CAR-T, combinations with immune checkpoint inhibitors, I think vaccines to prevent the disease, I think these are all things that I hope we'll see move forward.

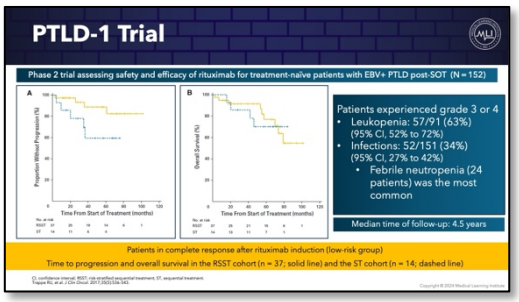
Dr. Voorhees: We're trying to target a lot of these approaches through some of the work we're doing at OSU. I think in general, our focus has been on reducing toxicity, avoiding chemotherapy when we can for these patients, and so we have some frontline trials looking at combination antibody-based therapies to hopefully achieve more remissions and complete remissions without chemotherapy.

Things like tafasitamab combined with rituximab are approaches that we're using. We're also excited about the bispecific antibodies. We have an investigator-initiated trial looking at epcoritamab in the relapse setting for PTLD patients, not specifically for EBV+ disease. I'd also agree, I think the data that we're seeing coming out of the ALLELE trial is very promising, and certainly for EBV+ patients who need to move on to that therapy, it's a great option for patients.

Ms. Featherston: You mentioned this too, Dr. Mahadeo. How do you evaluate the potential of CAR T-cell therapy and the treatment of EBV+ PTLD?

Dr. Mahadeo: Again, there are emerging case reports and some data on sequential CD19, CD22 infusions of CAR-T directed at LMP1. I think these are all things that are being worked on. This is a super rare disease, and so proving efficacy is going to be challenging, but I think it's sort of still exciting in particular when nothing is a home run right now.

Dr. Voorhees: Yes, I agree. I think there have been some multicenter CAR T-cell databases published in the last year or two after solid organ transplant. It is feasible to potentially get these patients through a CAR-T product, but reducing immunosuppression becomes the biggest challenge. Potentially collecting them on steroids, getting approval to do so, is still quite a challenge for these patients. It is possible to do. Outcomes may not look quite as great as you would think for the relapsed diffuse B-cell lymphoma setting, but there are still some long-term responders.

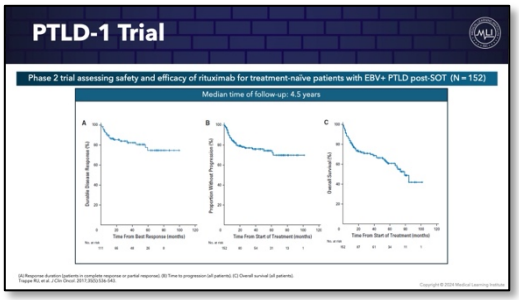


PTLD-1 Trial

Data's a little bit different in solid organ transplant. PTLD-1 was a phase 2 trial looking at the safety and efficacy of rituximab for treatment naive patients with PTLD in general, but many of the patients had EBV+ disease after solid organ transplant, so this is the biggest trial that we have for frontline PTLD with over 152 patients enrolled.

The study initially started with sequential treatment, so patients got rituximab monotherapy and then progressed right into chemoimmunotherapy for four cycles, and then later was amended to have more of a risk-stratified approach where, like we talked about before, we had induction rituximab for four weeks, repeat scans. If the scan looks good, then they continue on with rituximab therapy. If not, then moving on to chemotherapy.

You can see on this graph that the progression-free survival difference on the left and the overall survival difference on the right. There's actually no difference between sequential therapy in the blue line and the risk-stratified approach in the yellow line. The trial moved forward with more of the risk-stratified approach going forward after this.



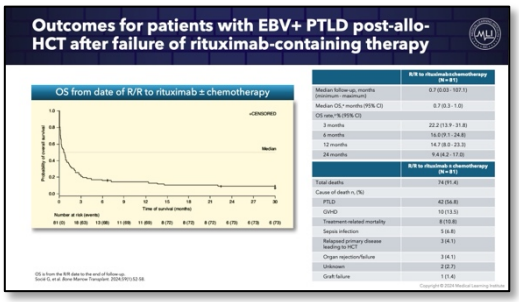
PTLD-1 Trial

Here we show the state and durable disease response, progression-free survival, and overall survival for the full cohort of the 152 patients.

You can see here that patients who, regardless of whether or not they did need to move on to chemotherapy or were successful with rituximab alone, the durable response rate is very good. Progression-free survival also levels out, and patients who achieve a complete remission at the end are often successful in continuing that remission. We do see that overall survival continues to fall over time, and that's likely due to a number of factors with patients and comorbidities after solid organ transplant.

Another important factor that I don't think we have on this slide is just that there was a significant difference in patients who were able to go through rituximab monotherapy and then consolidate that with more rituximab therapy. Those patients did the best out of everyone on the trial, and that was about 25% of the patients. We knew from this trial that still, three-quarters of the patients do end up moving on to a chemotherapy-based approach, but there is about a quarter of patients we can spare from chemotherapy, and really, we're focused on trying to figure out how we can increase that number of patients at this point.

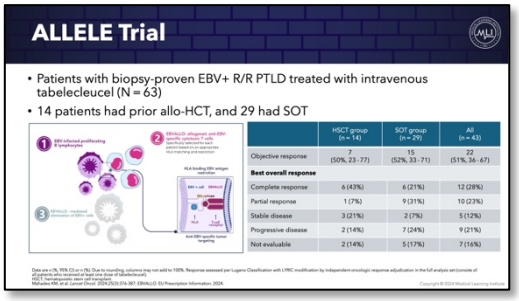
I'll just say one last thing about that data. If you look at the toxicity rates and the Grade 3 and 4 infection, Grade 3 and 4 cytopenia is pretty significant, and there was about an 8% treatment-related mortality rate on this study, which is lower than what we see in other studies where we see, actually, almost a 10% treatment-related mortality with chemotherapy-based approaches for PTLD. That just really highlights the importance of how toxic chemotherapy can be to these patients, and the need for newer therapies with less toxicity than chemotherapy.



Outcomes for Patients with EBV+ PTLD post-Allo-HCT After Failure of Rituximab-containing Therapy

Dr. Mahadeo: Thinking of the outcomes for PTLD post-allotransplant after failure of rituximab, alluded to this before, but this was a multi-center retrospective study and included about 81 patients. You can see that the median overall survival for patients who failed rituximab in the allo-HCT

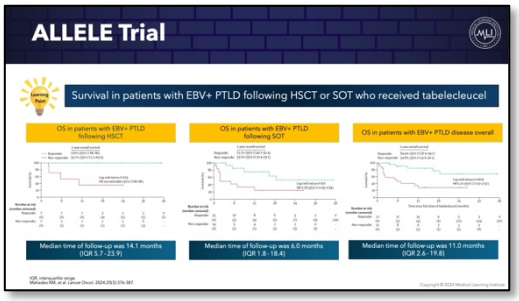
setting was 0.7 months, so that your one year at 12 months, your overall survival was only 14.7%. The causes of death in this group were by and large PTLD, GVHD, and treatment-related mortality. Again, just emphasizing the point that the response to rituximab is important, and if you fail that, they're really poor survival.



ALLELE Trial

Taking that into account, the ALLELE Trial was an international multi-center open-label Phase 3 trial, and it included patients with biopsy-proven EBV-PTLD who, in the HCT setting, had already failed rituximab. In the solid organ transplant setting, they would have failed rituximab, plus-minus chemotherapy. Tabelecleucel was used as a T-cell immunotherapy for these patients. This is sort of a third party, it's an off-the-shelf allogeneic CTL product that is used. Patients got them, a cycle would have been at day 1, 7, 14, and then you would have a response assessment between day 21 and 30.

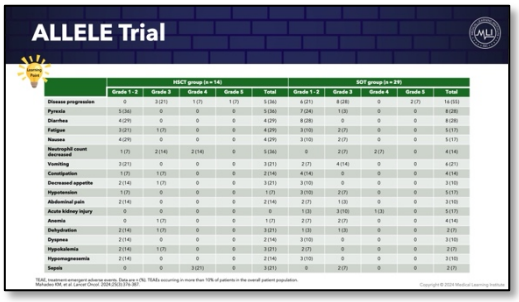
You can see that in the HCT setting, or the solid organ transplant setting, that you had objective response rates of about 50% overall and a clinical benefit. If you define clinical benefit as a complete response, a partial response, or stable disease, again, by and large, over 50%. On this study, 14 patients were allo-HCT patients, 29 had solid organ transplant prior, and again, they had to have failed rituximab or rituximab and chemotherapy.



ALLELE Trial

If you look at the survival in these patients, so again, if you think, if you remember, if you failed rituximab in the allo-HCT setting, your one-year survival was 14%. On that first panel, you see that the overall survival, if you're a responder at one year, was 100%. The median survival in the study has not been reached. In the solid organ transplant setting, the one-year survival in responders is 75%. Then for that combined cohort, you have an 84% survival rates.

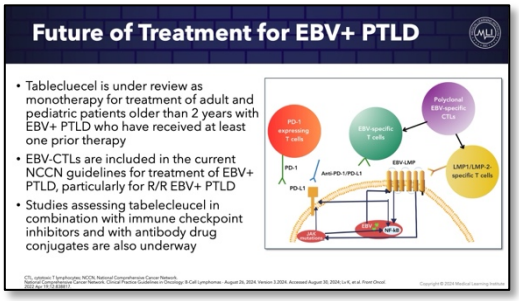
I think this is a clinical benefit was important, and again, intuitively, responders do better than non-responders. Particularly important for a disease where there's no standard therapies if you failed the first line.



ALLELE Trial

Ms. Featherston: You can see here that it was really pretty well-tolerated among both the stem cell transplant and solid organ transplant patients. The only grade 5 effects that we had were disease progression, which were not attributable to the infusion. Other than that, we did have some neutropenia in both groups, but most of the side effects were grade 1 or 2, and pretty general.

Dr. Mahadeo: In terms of treatment-emergent adverse events, so serious treatment-emergent adverse events were reported in about 53% of the patients. There were five fatal treatment-emergent adverse events, but none of them were related to the tabelecleucel product itself. There were no reports of tumor flare reaction that had been reported in some prior single-center studies, but none was seen in this study. There was no CRS, there was no ICANs. IL-6 and TNF levels were looked at. They did not rise from baseline, consistent with the fact that we didn't see CRS or ICANs. There was no transmission of infectious diseases, marrow rejections, or infusion reactions. In terms of AEs of special interest, there was no graft-versus-host disease seen or solid organ transplant rejection that were reported as related to the product.



Future of Treatment for EBV+ PTLD

When you think about the future treatments for EBV-PTLD, tabelecleucel is under review as a monotherapy for treatment of adult and pediatric patients. Again, in the study, there was no age limit. If you had the diagnosis, you were eligible. If you're older than two years is what it's under review for now with EBV-PTLD, who received at least one prior therapy. EBV-CTLs, as you saw, were included in the current NCCN guidelines.

Studies assessing tabelecleucel in combination with immune checkpoint inhibitors and antibody drug conjugates are underway.

Dr. Voorhees: I think the key takeaways from today, hopefully, first, I think, obviously, a thoughtful review needs to be taken in terms of the disease epidemiology and diagnosis of EBV+ disease is critical and essential to identifying these patients and selecting the best therapy for them and improving outcomes. Takeaway two, obviously, we need to consider the challenges and complexities to both diagnosis and treatment. This can help us inform better treatment options for these patients in the future. Takeaway three, as data for EBV+ PTLDs continue to evolve, education on the latest evidence and guidance for treating these patients is really important. We're starting to see some movement and guidelines that really haven't changed for quite a long time. It's an exciting time to move the field forward for these patients.

Ms. Featherston: What about immune checkpoint inhibitors? What role do you think they play in the management?

Dr. Voorhees: I think there's been several studies and case reports coming out about checkpoint inhibitors, and I think this disease specifically has been linked to higher levels of PL1 expression. Mechanistically, I think it makes sense to look at checkpoint inhibitors. Certainly, there can be efficacy of these therapies, but I think the biggest risk and concern obviously is about allograft health and the possibility for either rejection or loss of the graft, which I think the data is still out a little bit on how significant that is or is not, but certainly, the therapies could be successful, especially in the relapsed setting.

Dr. Mahadeo: Sarah, I guess just wearing your nursing hat, what role does patient quality of life, you think, play in evaluating success of new treatments as we evaluate all of these?

Ms. Featherston: I think that we need to look at patient quality of life, things like where are these treatments, are they only at specialized centers, are these patients having to travel, are there long inpatient stays, educating the family and the patient. All of these things to make sure that they're making those informed decisions on whether or not this, whether it be standard care or a clinical trial, whether this treatment is right for them.

Dr. Mahadeo: All right, well, thank you again for participating in the symposium.

Dr. Voorhees: Thank you.

Ms. Featherston: Thank you.