



EPISODE 2 | MAKING THE RIGHT SELECTION: EXPERT GUIDANCE ON TREATMENT SEQUENCING OF T-CELL MEDIATED THERAPIES



Loretta Nastoupil, MD: Welcome to this *Med Table Talk™* series on Lymphoma: The Power of The Community Translating Innovations into Care in non-Hodgkin and Hodgkin Lymphoma. This is Part 2 of a 4-part series entitled, "Making the Right Selection: Expert Guidance on Treatment Sequencing of T-cell Mediated Therapies." My name is Dr. Loretta Nastoupil from the University of Texas, MD Anderson Cancer Center, and welcome back to my fellow colleagues who will, if you would please

quickly reintroduce yourselves.

Ann LaCasce, MD: Thanks for having me. My name is Dr. Ann LaCasce from Dana-Farber Cancer Institute in Boston.

Amitkumar Mehta, MD: Hi, happy to be here. I'm Dr. Amitkumar Mehta. I am at the University of Alabama at Birmingham.

Dr. Nastoupil: Thank you, and let's get started.

It's been interesting to see over the last few years that we have now adopted a shared decision-making model between clinicians, the sort of provider team, and patients. And I think it's an important step forward, and it's an important aspect in terms of patient autonomy.

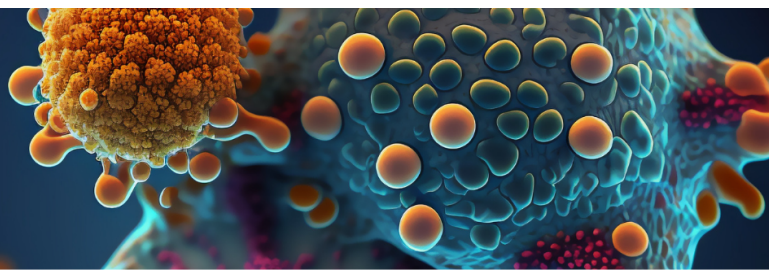
It does create some areas for unmet need. For instance, as the treatment landscape evolves and we have more and more therapies available, how do we as the healthcare team educate patients about the safety and efficacy of a given therapy, how that therapy fits into the current treatment landscape and what the implications might be for subsequent therapy if that treatment is ineffective, both in terms of, "Well, what will we do next?" and what would be the impact in terms of quality of life if they need subsequent therapies?

EFFICACY OF CAR T THERAPY IN R/R NHL		
Disease	Product	Efficacy ORR, EFS/PFS
Diffuse large B-cell lymphoma (DLBCL)	• Axicabtagene ciloleucel	83%, 8.3 months
	• Lisocabtagene maraleucel	73%, 10.1 months
	• Tisagenlecleucel	46.9%, 3.0 months
Mantle cell lymphoma (MCL)	• Brexucabtagene autoleucel	93%, 25.8 months
	• Lisocabtagene maraleucel	83.1%, 15.3 months
Follicular lymphoma (FL)	• Axicabtagene ciloleucel	89%, 39.6 months
	• Tisagenlecleucel	86%, 57.4% @ 24 months
	• Lisocabtagene maraleucel	95.7%, 91.3% @ 12 months
Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)	• Lisocabtagene maraleucel	95.7%, not reached

Efficacy of CAR T Therapy in R/R? NHL

And so, with that in mind, I think the, let's walk through the emerging T-cell engagers in terms of bispecific and CAR T-cell therapy for the management of relapsed/refractory large B-cell lymphoma, highlighting on some of those key aspects.

And I think the first place to recognize is if you don't have an approved indication with some of these therapies, because they're very resource-intensive, generally they're not going to be on the table. And so, making sure that



patients and caregivers recognize where these therapies are currently FDA approved and why sometimes we don't offer them, because I've been in that situation where I have a newly diagnosed follicular lymphoma patient who is a little perplexed that we're not talking about CAR T as an option. And so, making sure that we all acknowledge where they're currently approved, and you can see on this slide we have three FDA-approved products in that third-line or later space for diffuse large B-cell lymphoma, based off of single arm, phase II studies.

Two of these three have a broader application now in that they can be considered in second line. We have approvals for mantle cell lymphoma, generally for the post-BTK inhibitor space and then approvals for follicular lymphoma for those patients who progressed on alkylators and CD20 antibodies in that third-line or later space.

SAFETY OF CAR T THERAPY IN R/R NHL			
Disease	Product	CRS	
		All (severe), time to onset & resolution	Neurotoxicity
Diffuse large B-cell lymphoma (DLBCL)	• Axicabtagene ciltauceel	92% (6%), 3d, 7d	60% (21%), 7d, 9d
	• Lisocabtagene maraleuceel	49% (1%), 5d, 4d	12% (4%), 11d, 6d
	• Tisagenlecleucel	61% (5%), 4d, 5d	10% (2%), 5d, 9d
Mantle cell lymphoma (MCL)	• Brexucabtagene autoleuceel	91% (15%), 2d, 11d	63% (31%), 7d, 12d
	• Lisocabtagene maraleuceel		
Follicular lymphoma (FL)	• Axicabtagene ciltauceel	82% (7%), 4d, 6d	59% (19%), 7d, 14d
	• Tisagenlecleucel	49% (0%), 4d, 4d	37% (1%), 9d, 2d
	• Lisocabtagene maraleuceel	52.2% (0%), 6d, 3d	17.4% (4%), 8.5d, 2.5d
Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)	• Lisocabtagene maraleuceel	83% (9%)	46% (20%)

Safety of CAR T Therapy in R/R NHL

It's important to recognize beyond efficacy, which we're clearly enthusiastic about, is that these therapies come with some downside; and generally, the downside is the acute toxicity in the form of cytokine release syndrome or neurologic toxicity. And though they vary across these single-arm, phase II studies, you have to be careful in interpreting that because some of the grading and management varied. And we've gotten much better at that over time, and so we're seeing, in general, lower rates of grade 3 or higher CRS or neurologic toxicity.

But, for instance, if you're considering follicular lymphoma where the toxicity might be under more scrutiny, given the available treatment options, I do think that these are important considerations.

BRIDGING THERAPY FOR PATIENTS AWAITING CAR T-CELL MANUFACTURE

Bridging Therapy

- Designed to reduce tumor burden, relieve symptoms, or stabilize disease while awaiting CAR T manufacture
- Not "required" for all patients and restricted to certain regimens on some clinical trials, but often needed to control disease while awaiting CAR T manufacture
- Can also serve to maintain functional reserve during manufacturing period
- However, as with any chemo or radiation treatments, can have side effects, so typically providers attempt to limit to what is absolutely necessary

Recent evidence suggests:

- Lower disease burden may result in better response to CAR T, and may reduce likelihood of CAR T-related side effects (that we will discuss in coming slides)
- It is beneficial to avoid certain medications (that target the same protein/targets that the CAR T target, other immune-targeting medications) just prior to CAR T therapy

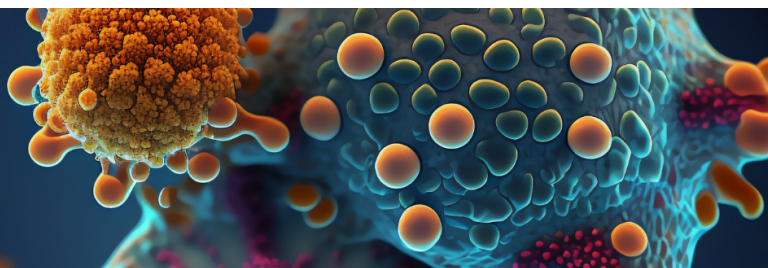
****Important considerations:**

- Maintain frequent communication with patient, oncologist and manufacturer to plan when bridging therapy is advised (if applicable), how long the bridging period is anticipated based on manufacturing and infusion (limited-pool patient responsiveness)

Bridging Therapy for Patients Awaiting CAR T-Cell Manufacture

Shared decision-making as it pertains to bridging therapy also takes into account the community oncologists. Oftentimes patients would like to return home while they're awaiting manufacturing, and the lymphoma-directed therapy can be administered locally. So, it does create some additional dynamics in terms of when that therapy is initiated, what therapy is administered.

But I do think that more effective bridging strategies has led to improvement in outcomes post-CAR T.



EFFICACY OF BISPECIFIC ANTIBODY THERAPY IN R/R NHL		
Disease	Product	Efficacy ORR, DOR
Diffuse large B-cell lymphoma (DLBCL)	• Glofitamab • Epcoritamab	56%, 18.4 months
		61%, 15.6 months
Follicular lymphoma (FL)	• Mosunetuzumab	72%, 22.8 months

Efficacy of Bispecific Antibody Therapy in R/R NHL

What about the bispecifics? Again, they do provide some advantages in that they're off the shelf, meaning they're IV or subcutaneous therapy that does not require patients undergoing apheresis and shipment of cells off to site for central manufacturing. But they also do come with some unique aspects in that they do require acute toxicity monitoring, particularly in the first cycle.

The efficacy looks to be quite favorable with these bispecific antibodies, all be it again in single-arm, phase II studies in that third-line or later space. And we have two now FDA approved for large B-cell lymphoma and one for follicular lymphoma with, again, more anticipated to be emerging.

SAFETY OF BISPECIFIC ANTIBODY THERAPY IN R/R NHL			
Disease	Product	CRS All, median duration, (range)	ICANS
Diffuse large B-cell lymphoma (DLBCL)	• Glofitamab • Epcoritamab	70%, 2d, (1-14d)	4.8%
		51%, 2d, (1-27d)	6%
Follicular lymphoma (FL)	• Mosunetuzumab	39%, 3d, (1-29d)	1%

Safety of Bispecific Antibody Therapy in R/R NHL

How do we navigate this? I do think that the schedule, in addition to the cytokine release syndrome, does factor into consideration; but I do think that, again, having several new options does provide a number of options for patients. And with these bispecific antibodies being something that the toxicity's clearly manageable and mostly confined to the first cycle, it does open the door for combination strategies, questions about optimal sequencing of therapy, and so, again, how do we share the

decision-making with patients?

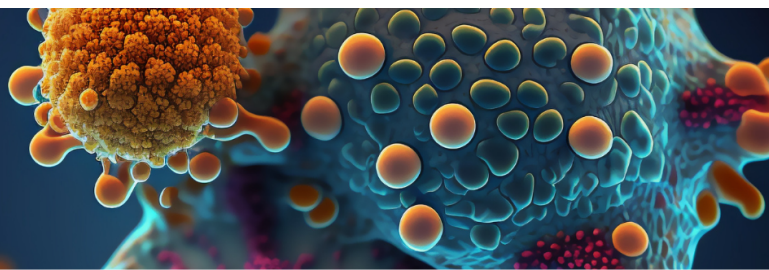
NEW AND EMERGING IMMUNOTHERAPY OPTIONS FOR R/R NHL	
Cellular Therapy Challenges	Possible solutions for effective outcomes
<ul style="list-style-type: none"> • Dual targeting CAR T (targeting multiple antigens to reduce risk of antigen-negative relapse) • New and improved autologous CAR T <ul style="list-style-type: none"> • Alternative manufacture strategies that enhance efficacy and reduce toxicity • Bispecific antibodies and combination therapies <ul style="list-style-type: none"> • CELMoDs • Allogeneic or "off-the-shelf" CAR T-cell therapies • Moving CAR T treatment earlier • Point-of-care manufacture (at clinical sites) 	<ul style="list-style-type: none"> • Expedite manufacturing process • More efficacious while being less toxic • Increasing access to CAR T-cell therapy at other sites • Diversity among participants of clinical trials • Telehealth visits • QOL analysis • Prospective cost effectiveness analysis • Modify reimbursement structure

New and Emerging Immunotherapy Options for R/R NHL

Are we now talking about just CAR T versus bispecific? Are we talking about bispecific plus CELMoD versus plus antibody drug conjugate? Do we consider it based off of line of therapy? Do we consider it based off of patient-specific request in terms of toxicity and impact on quality of life?

And so, with that, I'd like to get, you know, input from my colleagues here. How do you consider shared decision-making as a major factor? And we'll start with large B-cell lymphoma but also expand out into some of the indolent lymphoma subtypes such as FL and CLL. Amit, how do you approach this?

Dr. Mehta: It's very complex, and the reason I say that, you know, when we started, you know, it was very simple to tell patients that, "Hey, this is going to be a chemotherapy." Now, we will explain first the agent, the mechanism of action, what it entails into. And to be very honest, I've seen, and I'm sure that you must have seen it in your clinic also, which, you know, age group of patients we are looking at, right, because some of the age groups are younger. They're more attached to the media, their social medias, and etc. They're getting a lot of information, so they're already prepared. They're well-read. And, you



know, the other extreme that we see in the clinic is, "Well, doc, whatever you decide, we'll go with it." Right, so that is the two extremes that we have to deal with.

But at the end of the day, it takes a lot of time to explain the mechanisms of action of this agent, their maintenance, their side effects. So, spending a lot of time in the clinic discussing with the patient, as well as patient's relative, and afterwards coming to a conclusion that, "Okay, we're going to go with this treatment, and this is what we're expecting."

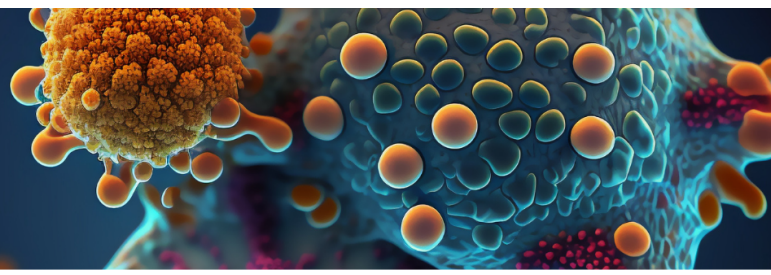
Especially with CAR T. There are so many steps, so I always like to have somebody with the patient because already the patient is under stress. The cancer has come back. I don't know how much they're able to pay attention to. So, I think having more members in the room helps. If somebody's taking notes, that's great because then they can keep up what we discuss and what we expect afterwards. Our navigators, actually, help a lot in that situation. Having them in the room is also critical because, you know, we have new navigator. They don't know about the process. It is better that we educate them what we expect so that they can educate the patient. So, the process has evolved quite a bit recently.

Dr. LaCasce: I think these patients come in, and it's, it's like the first discussion you have with someone who has a new diagnosis. There's so much information to cover, and I think it has to be reiterated. So, you know, maybe you have one visit; and then I agree, having an ONN or someone else follow-up with the patient and make sure that they really understand because what, I think we're not as good as physicians necessarily about telling people exactly what to expect on it.

You know, we sort of look at the toxicity data and, you know, "Oh, yeah, it's going to be this or this, low risk of that." But, you know, what does it actually mean for the patient as they're living through it, I think is something that, at least I'm not sure that I always convey that as well as I could. And I think, you know, having an awesome NP or having an ONN to, to meet with patients also helps a lot.

The other thing, I think, would be, you know, this, you mentioned quality of life; and I think that is so critical. But we don't have great ways of helping patients, I choose therapies and figure out like what is important to them. And, you know, what, you know, as, as you mentioned, maybe it's the driving thing. You know, I think that is a key thing for our older patients. "What do you mean I can't drive for two months?"

But it would be nice to have some sort of decision tool to be able to use with patients to help them understand what the pros and cons of various therapies are. I think sometimes, you know, if you're looking at second-line CAR, I'm going to push hard for that. And I think, you know, it's potentially curative. It's much, you know, much better than salvage chemotherapy transplant. So, you know, I think it depends on the setting, how much I'm going to push someone to try to encourage them to consider a therapy. But, yeah, I think it's a group approach; and it's, it's got to be reiterated many times to make sure that the patients actually have a sense of what to expect.



Dr. Nastoupil: Yeah, I think that's really critical; and I think one thing that I always start off these discussions with is making sure I know what is important to them because, generally speaking as an oncologist, efficacy is always important to me because I know that if I can't get control of the disease, that's clearly going to have a negative impact on not just longevity but clearly quality of life, and particularly with the aggressive lymphoma subtypes.

But I also recognize that sometimes patients may have other priorities, and particularly we're talking about a group of patients that have now progressed after frontline. And so now their perspective may have shifted. And maybe it's important to them to have time to get their affairs in order, and so I've been in many situations where I want to move as quickly as possible to CAR T because I know that's going to likely improve or give them the best chance at efficacy. But there may be times where they need time to get certain things addressed before they're willing to move forward.

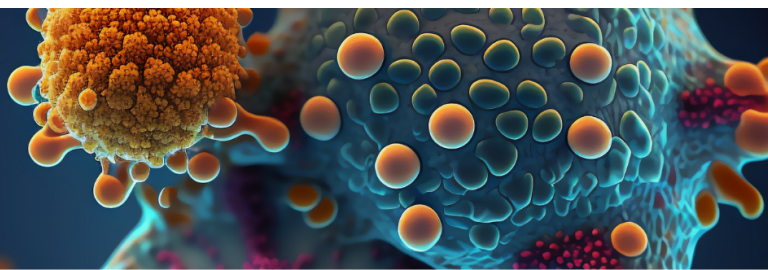
And so, I think we do need better tools of helping them sort of gauge, okay, if I prioritize time away from treatment right now, what does that mean down the road in terms of quality of life and impact on efficacy of that next line of therapy? And I think in general, you know, as much as we want to continue to provide optimism and enthusiasm about the future, sometimes we also have to acknowledge that we're oncologists; and sometimes patients have bad outcomes. And so, making sure that we're transparent about that and take into consideration what's important to them as we're lining up their next line of therapy because no one wants to be in a situation where we keep heading down the path of more and more treatment, nothing turns around the bad disease, and now we've robbed them of whatever time they may have had left. And so, kind of a negative spin on it.

Now, let's flip the coin and talk about, okay, indolent lymphoma. That's usually not as big of a factor in my decision-making. That's where I really do weigh what is their goals in terms of quality of life, where they want the treatment, whether it's outpatient versus inpatient, how much time they're willing to give up from careers and family members. And so, I do think the disease also factors into that. Amit, what are your thoughts about that?

Dr. Mehta: Like we talked about say mantle cell lymphoma, you know, a different, a totally different biology. So as CLL, in CLL most of the patients are older population. So, taking them to an intensive therapy in that situation, you know, their goal, it is critical.

One other thing that, you know, all across the board recently that has come up, I have one patient who actually went to CAR T, had neurotoxicity, and it was not that, but up to grade 2 to an extent that she had memory lapses and, you know, she was confused.

And she told me that for a period of time she was not there, and then she came back. And interestingly, she brought up a point that, you know, I experienced this. And if any of your patients wants to know more about this treatment, I'm happy to, you know, talk to them.

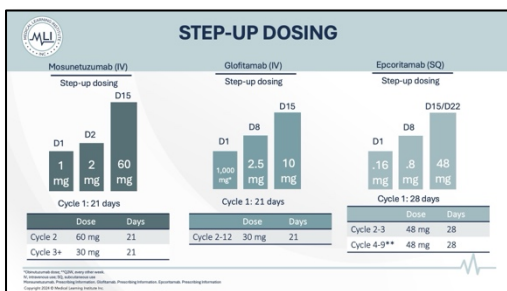


And before there also, we had one patient who was open to talk about it. You know, like we, we live in a world that anything that I buy, maybe on any website or online, I like to look at the reviews and what is the experience other people have with that, whatever I'm planning.

This is that era, right? People like to talk about it. "Hey, I'm, I'm planning to consider CAR T. What was your experience?" I think that has come up very nicely, and we had a couple of patients who talked to the patients who were going in CAR T, and they benefitted the most. So, I think that kind of, you know, disposition and negotiation helped them to understand whether it aligns with their preferences going through the treatment.

Dr. Nastoupil: And I think having input from somebody who's actually been through it is probably much more valuable than an oncologist just describing, as Ann alluded to, sort of our limited understanding of what the toxicity really is like.

So, let's talk, we've spent a lot of time about CAR T. Let's take a look at the practical implications of bispecific antibodies. And there are several that are approved in different indications. All currently have employed strategies to reduce the cytokine release syndrome, anticipating that then will lead to a broader group of patients that would potentially have access to this.



Step-Up Dosing

And one such approach is step-up dosing, so starting at very low doses at day 1. Just a little higher dose at day 2, day 8, generally speaking. And then you get to full dose by day 15. And with that approach, we have seen rates of grade 2 or higher cytokine release syndrome decrease.

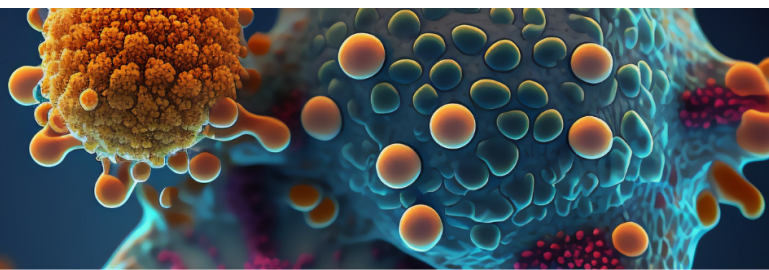
Grade	Management	Notes
Grade 1	Observe	• Early fever (within 72 hrs) or significant comorbidities can consider early tocilizumab.
Grade 2	Tocilizumab 8 mg/kg (Consider alternative agents after 2 doses) *No more than 3 doses in a 24hr period or 4 doses in total.	• For patients with early fevers or significant co-morbidities, consider early dexamethasone (10mg x1). • Patients not responding to tocilizumab should consider initiation of dexamethasone (10mg q12-24hrs).
Grade 3	Tocilizumab 8 mg/kg (Consider alternative agents after 2 doses) *No more than 3 doses in a 24hr period or 4 doses in total.	• Dexamethasone (10mg q12-24hrs) with tocilizumab initial tocilizumab. • For patients refractory to dexamethasone can increase to 20mg q6-12 hrs.
Grade 4	Tocilizumab 8 mg/kg (Consider alternative agents after 2 doses) *No more than 3 doses in a 24hr period or 4 doses in total.	• In dexamethasone refractory patients, consider high-dose methylprednisolone 2mg/kg q12 hrs. • For refractory patients consider alternative therapies.

Always look for infections and treat infectious complications, especially in neutropenic patients.

CRS Management

And we use a lot of terms like grading because that's how it's done in clinical trials; but grade 2 is generally somebody who's going to need IV fluids, supplemental oxygen, things like tocilizumab, and/or corticosteroids to try and address this toxicity. Grade 3 or higher is generally patients that are in the ICU that are needing pressor support, maybe even more aggressive oxygen support. And so, obviously, we'd love to keep patients out of the ICU and grade 1 or 2 if at all possible.

How do we manage these patients, and that's where Ann alluded to earlier. There is a white paper that's come out with guidance from people who were involved in the initial clinical trials to assist with the CRS management and, I think, in general, importantly, make sure the patient, the family members are aware of what we're watching for because most of these toxicities are not going to occur while they're in the



infusion center. So, this is a little different than infusion reaction. Where, we're anticipating this is going to happen while they're there. We're going to address it, and it's going to be resolved before they leave. And there are differences in terms of timing from infusion to onset to be mindful of, and generally that length of time lengthens as they get further into that first cycle of treatment. But generally, fever is going to be the first indication that we're dealing with cytokine release syndrome; and then the intensity of grading increases based off of whether or not they have hypotension or hypoxia.

We have traditionally borrowed our approach to management from the CAR T space and that we tend to utilize tocilizumab and/or corticosteroids as we get into those higher grades. But I'm going to pause here for a second and get both of your opinion. Ann, how are you approaching CRS right now, particularly for patients who might be home when they have that first fever?

Dr. LaCasce: We have a lot of debate about this, and I think you're right. I think we're moving away from using tocilizumab, even in grade 2, or definitely in grade 1. It's different than CAR T and using steroids can be very effective. If people just have fever, I think it depends on how comfortable they are monitoring their blood pressure and their pulse at home and their symptoms with a low threshold to go to the emergency department if there's any question.

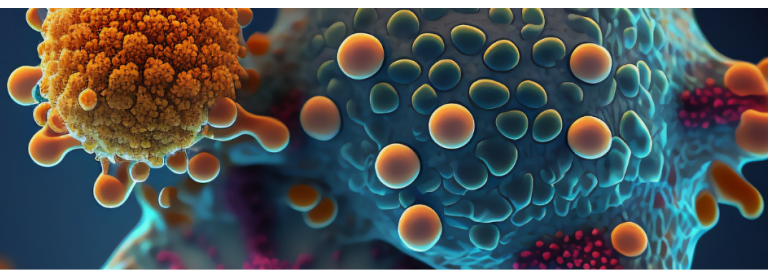
But with grade 2, I think steroids alone, I think, are the, you know, pretty much becoming the standard and I think this is going to allow this therapy to go to the community a lot more readily because this need for having tocilizumab onsite can be a big issue. It's an extremely expensive drug, and I don't think we need to use it nearly as much with the bispecifics as we do with, with CAR. But I think for grade 2 or higher, obviously, patients are going to need to be at the hospital being carefully monitored to make sure that they're going to turn around.

But I think we're getting a lot of experience with exactly when to expect these toxicities with each of the agents. And the more we do this, the better it's going to get. And I'm hopeful that we're going to be able to keep most of the patients out of the hospital in the near future with the bispecifics.

Dr. Nastoupil: Amit, anything else to add?

Dr. Mehta: Well, one of the approaches that we have done is, you know, me and my nurse practitioner, have come up with a flowchart and a log of the blood pressure, you know, and vitals. So, most of the patients have, you know, COVID time, many of the patients bought the blood pressure instrument, thermometer, and, you know, pulse ox. So, they have it.

And we provide this document which actually lays out as mentioned that most of those things we can manage at home. So, they chart their blood pressure and, you know, all the vitals. They also have dexamethasone prescription. They also have diphenhydramine or acetaminophen at home. And if they have fever, the first step is to take, you know, acetaminophen and make sure that you're not dropping your blood pressure, dropping your oxygen level.



And they kind of manage with the help of the on-call doctor. When they feel that they are tipping into grade 2 or grade 3, that's when the on-call doctor would refer them to the ECC, rather than going to the emergency room. That way we bypass the emergency room, and ECC or extended care clinic has tocilizumab; and with the help of the patient and the caregiver, be managed at home. So, that's the approach which has, you know, worked out very well for us.

Dr. Nastoupil: That's really intriguing. I think, as you both said, we're just going to get better and better at this CRS management. I think some challenges still lie in the neurologic toxicity which, fortunately, we're seeing very low rates currently with the bispecific antibodies but maybe still something that induces quite a bit of fear and concern in patients when we're talking about CAR T-cell therapy and particularly some that are associated with higher risk of that grade 3 or ICANS.

ICANS MANAGEMENT		
Grade	Neurotoxicity	CRS + Neurotoxicity
1	Supportive care (+ steroids)*	Supportive care (+ tocilizumab)
2	Steroids (dexamethasone or methylprednisolone)	Tocilizumab + steroids (dexamethasone)
3	Steroids (dexamethasone)	Tocilizumab + steroids (dexamethasone)
4	High-dose steroids (methylprednisolone) ICU/critical care	Tocilizumab + high-dose steroids (methylprednisolone) ICU/critical care

*High burden, high-risk products, older comorbidities, etc.

Neurology consultation
Low threshold for repeat management (if repeat at time of crisis)
Multidisciplinary team approach

ICANS Management

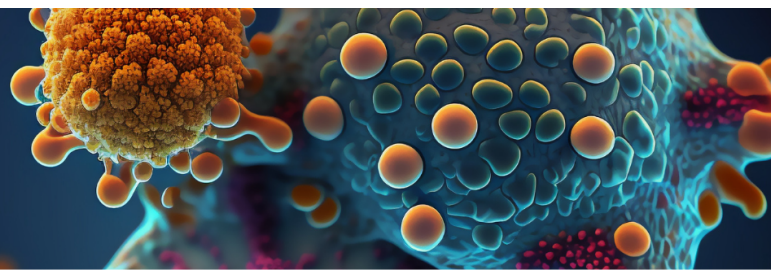
And I also appreciate, Amit, your description of that case where if somebody had grade 2 ICANS, because I've also heard similar patients describe that they know they're not fully making sense, but they recall what it was going on. They just weren't present in real time.

But I do think there's also some PTSD that's experienced oftentimes by the family members because of the dramatic shift that happens. They're fine one minute. All of a sudden, they're completely a different person and then that shift that goes right back to being normal again.

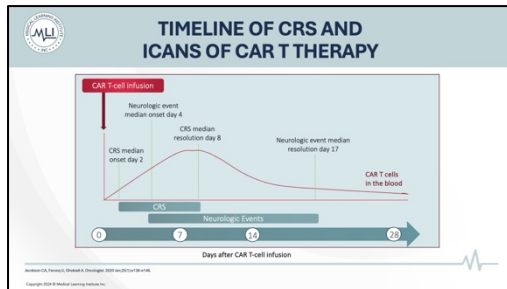
And so, again, I think that's an area where we could potentially improve upon our management which is the ICANS or neurologic toxicity which generally is primarily driven by corticosteroid utilization, sometimes plus/minus tocilizumab if they have concurrent CRS. And again, in my experience thus far with the bispecifics, I think that is much less frequent in occurrence and just a different scenario altogether than what we see with CAR T.

Dr. LaCasce: Can I add one thing for mantle cell? You know, brexucabtagene is probably the worst offender in terms of neurotoxicity in mantle cell, particularly in people who have a lot of disease. So, I think warning those people it happens early and often; and we should, hopefully, liso-cel is going to the FDA very soon, and the safety profile of that agent looks really good in mantle cell. So, hopefully, we'll be able to shift away from that for some of our patients.

Dr. Mehta: Now, I'm glad that you brought it up, Ann. And you're right, the neurotoxicity with brexu-cel is very high; and sometimes that actually, you know, I make a decision of bridging based on that. And sometimes I'll use, you know, cytarabine or intrathecal even going into CAR T. And I've seen that has helped in some patients to reduce the ICANS rate.



But you're right. It is a problem. I think the leukemic phase, we are seeing more ICANS with brexu-cel, but that is a very important point.



Timeline of CRS and ICANS of CAR T Therapy

Dr. Nastoupil: So, we've just spent a lot of time talking about CRS and ICANS, which are generally the acute toxicity that happens in the first mostly 14 days post-CAR infusion in the first cycle with bispecific antibodies. But I think there's something else to at least be mindful of. Sometimes patients don't have full recovery, particularly those that have high-grade ICANS within the first 30 days. You can sometimes see sort of a tail of that

curve where it may take them up to two to three months to be totally back to normal. I've seen that particularly in older, frailer patients. Then, again, they may have struggled using their smartphone for a period of time.

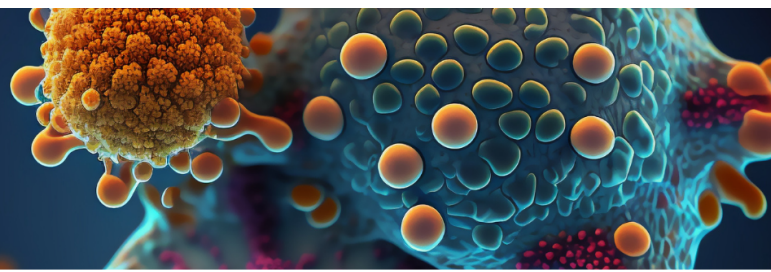
The other thing I think we also need to be mindful of is the infectious complications that can definitely arise. And again, depending on the construct with the CD28, CD19 auto CARs, we're seeing about 20% to 40% of patients having sort of this biphasic count recovery. So, they drop with the LD chemotherapy. They recover, and then after day 30, they drop again. And then they can have these prolonged cytopenias that definitely increase their risk for infectious complications.

So, I'm curious about my two colleagues here are trying to develop sort of algorithms and guidelines for how to mitigate infectious complications, either through the use of VZV prophylaxis, PJP prophylaxis, and we're all a little bit struggling with how to handle vaccine utilization given many of these patients will have prolonged B-cell depletion. So, what are your thoughts about how to best mitigate the risk for infection?

Dr. LaCasce: Using PJP prophylaxis with Bactrim and VZV prophylaxis helps a lot. I think the one question I would love to hear what both of you do with regard to IVIG repletion. A lot of these patients are hypogammaglobulinemic, but if they're not getting recurrent bacterial infections or even recurrent viral infections, I will start them. But I don't generally give it unless people are under 400 and symptomatic. But I would love to know what you all do.

It's really the viral infections and I think being cautious, particularly in the winter. Like we saw last winter when people had not had exposure to a lot of common viral illnesses that hadn't been a problem during COVID when everyone was wearing a mask; and then everybody was getting sick all the time, and it was really frustrating.

Dr. Mehta: Aggressive monitoring and prophylaxis, those are the two strategies that I use. And again, you know, post-CAR T, cytopenias, neutropenia, you know, liberal use of growth factor when needed. IVIG repletion.



Well one other thing that I also noticed is CMV reactivation. I have a couple of patients, you know, they'll have cytopenias and you monitor, and you don't have any idea. Maybe it's post-CAR T. Let's try this. But then two patients were CMV-positive, and they were treated.

So, I think, you know, monitoring is a key; and, you know, growth factors and IVIG replacement with prophylaxis is very, very important. As Ann mentioned, there were many viral, you know, infections to COVID and triple threat, whatever you want to say, last December was pretty bad on some of the patients. So, I always recommend that at least for first few months, make sure that you wear mask if you go out in public in, you know, crowded places. That would definitely help.

Dr. Nastoupil: I'm really excited to have an opportunity to talk with Dr. Caitlin Murphy. So, Caitlin, I'm so interested to hear sort of your perspective on what are best practices to prevent and monitor some of these unique toxicities that are related to CAR T-cell therapy and bispecific antibodies?

Dr. Caitlin Murphy, DNP: Of course. So, I think that it starts with the initial phase of prevention in terms of patient education and really informing the right patient for the right therapy, in terms of matching what their care decisions are and the feasibility of the care opportunity. So, I think finding the right patient for the right therapy is essential.

And I think that a lot of it is laying out that foundation of where the care is, is being provided and, and kind of the social aspects of their care in terms of caregiver support.

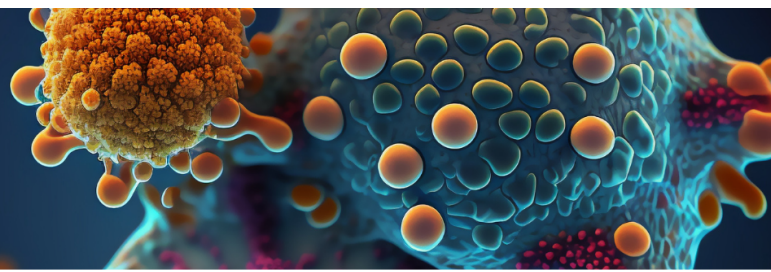
And I think one piece that we often talk about, you know, caregiver support in a heavy load with the CAR T therapies, which are fully warranted. I think the piece with bispecifics is that in that emergent need for evaluation, who can readily bring them, oftentimes when they're home alone or maybe someone isn't close by to be able to kind of help with that expedited evaluation?

I think the other piece too in terms of monitoring is, is the onus not so much on the patient all the time but in that collaboration that, having that vested interest that we want to keep them at home where they, where they want to be.

And so how do we do that? How could we partner and make sure that they know how to take their blood pressure, they know how to take their temperature? They're doing it with all of those medications easily at hand, so maybe it's at their first visit they know to have on hand Tylenol and similar products and a pill-in-pocket type of approach with corticosteroids.

I think the other piece is understanding their other preexisting comorbidities. A lot of patients already have a lot of other implications, and so whether they're a diabetic or have kind of poor glycemic control and they're on steroids, integrating those types of pieces.

Dr. Nastoupil: You bring up a really good point, and we do see quite heavy use of corticosteroids in the first sometimes several weeks to try and mitigate the CRS. What are you counseling patients in terms of



those with preexisting diabetes? How does, who are they communicating with whenever all of a sudden, their glucose is several hundred? Is it the oncologist? Are you pulling in their primary care or the endocrinologist? I'm really curious how you're handling those situations.

Dr. Murphy: And I think we're still doing some investigation into kind of best practices for this piece. I think oftentimes we kind of look at a blood sugar in the 150s or 200s, and you're like, "Oh, that's not great, but..." So, I think, oftentimes it's informing patients that they may have these changes if they're someone that definitely is checking their blood glucose on a regular basis. But in those emergent cases, it's utilizing some of our already established protocols when they arrive to patient, arrive to the clinic in a hyperglycemic state.

And then, you know, fortunately, we have a great partnership with our endocrinology team; but then it goes back to communication with the primary care team because they may not need steroids for a long period of time on the bispecifics, you know, and that aspect. But they may need it for the duration of their therapy, depending on the tolerability. So, it's a shared care across, you know, interprofessional teams as well as along with the patient and caregiver.

And I think the other element is exercise and, and diet and kind of trying to highlight some of those pieces that can kind of empower them to be able to take some action and so that they feel as well as they can during these therapies.

Dr. Nastoupil: Such important insight, and again, so happy to have you with us to try and understand how we implement shared decision-making, particularly as it pertains to these newer therapies with unique toxicities.

So, what, let's conclude with our key takeaways. And again, in a perfect world, where are we and what would you like to see improved upon? And Caitlin, we'll start with you.

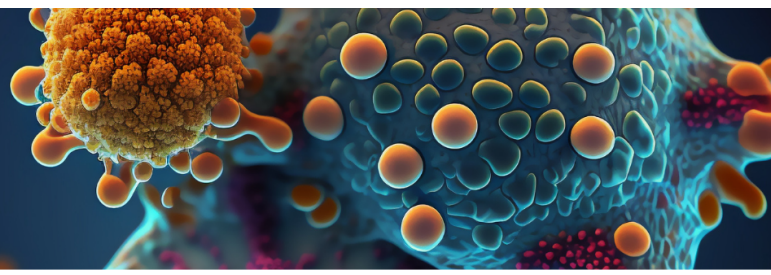
Dr. Murphy: I think that it's really laying out the framework of the whole treatment landscape. And so, giving patients a really great understanding of what happens in two to six months, and I think having that really clear picture for our patients and having some self-care strategies that they really can feel empowered to be a part of their care and find the best treatment modality that will give them, you know, best outcomes.

Dr. LaCasce: You know, I think being honest with our patients about what to expect, we all see these patients we know are not going to do well. Likely they have very high burden disease, so really trying to set expectations and involve the caregivers. But highlighting, you know, trying to empower people to make the best decisions for themselves and their families.

Dr. Mehta: It's an exciting time. There are, you know, good agents out there for the, for the treatment of aggressive lymphoma. But at the same time, I think we have to tailor the education and resources for education that we have for patients. And I think that's a task that we will be, probably will have to be



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master at, have to discuss these complicated treatments and their side effects. So with, you know, great outcomes. But hopefully, we'll, we'll get there as we go further.

Dr. Nastoupil: I think the key in my mind is really awareness, making sure that patients, family members, and community oncologists are aware of these new therapies, again recognizes a rare disease subtype.

What I'd love in a perfect world are better tools, as Ann highlighted earlier, to really understand how do patients want to hear information. What's important to them versus what's important to us? And how do we sort of find some common ground so that we know that we're informing them when we expect them to share in the decision-making.

So, again, really appreciate all of your comments.

I really enjoyed our discussion today, Dr. LaCasce and Dr. Mehta, and thank you to our special guest, Dr. Caitin Murphy. Thank you for joining for Part 2 in this series. If you haven't seen Part 1 of the series, be sure to check that out. Stay tuned for Part 3 where we will discuss taking a team approach. "Community-based Practices at the Forefront of Non-Hodgkin and Hodgkin Lymphoma Care" and our final part where we will discuss, "Checkpoint Conversations: Integrating Immune Checkpoint Inhibitors in Hodgkin Lymphoma."

For additional resources, please see the activity website. To claim credit, please complete the post-assessment questions and evaluation. Take care.